THE EFFECTS OF MATERNAL POLYUNSATURATED FATTY ACID CONSUMPTION DURING PREGNANCY ON THE INFANT'S COGNITIVE DEVELOPMENT

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ABSTRACT
The unique structure of polyunsaturated fatty acids (PUFAs) and their high concentration levels in the brain suggest PUFA availability plays a vital role in the development of human brains while in utero and in the first few months of life. Exactly how important PUFAs' role is in infant brain development is still unclear. It is known that the pregnant mother’s PUFA consumption is the primary supply for the fetus; however pregnant women often decrease their fish intake, the richest PUFA food source, for fear of mercury exposure. Observational studies that looked at varying levels of maternal fish consumption generally found that children of mothers who consumed more fish scored higher on tests evaluating brain development. Experimental studies on the other hand had inconsistent results when looking for an association between maternal fish oil supplementation and infant mental development. This lack of a definitive conclusion suggests a need for further research to explain the reasoning for the differences in these results as well as to bridge the gap between the findings. A more thorough understanding is necessary in order to provide pregnant women with the best information and recommendations on what to eat during pregnancy.
The Effects of Maternal Polyunsaturated Fatty Acid Consumption during Pregnancy on the Infant’s Cognitive Development

Introduction

While an infant is in utero, it is solely dependent upon the mother for nourishment. It faces many potential obstacles to receiving adequate nutrition such as inadequate maternal diet. A pregnant woman must ingest a balanced diet from the beginning of pregnancy to assure that her fetus has a sufficient amount of nutrients. A nutrient in particular that is critical for the fetus which pregnant women are often deficient in is polyunsaturated fatty acids (PUFA). Specific PUFAs such as docosahexaenoic acid (DHA) are for the development of many organs including the eyes, brain, and neural tissue as they provide elasticity to cell membranes (Blanchard, 2006). DHA is accrued in the brain during fetal development and is associated with learning and memory through its influence on neuron development, growth, and survival (Cao et al., 2009). DHA concentrations in the brain throughout life are largely dependent on the initial supply from early life. The brain is one of the first organs to develop and undergoes a critical growth period during the last trimester of pregnancy and the first few months after birth (Helland, Smith, Saarem, Saugstad, & Drevon, 2003). PUFA stores must be built up in the fetus during early stages of life as they are necessary for the development of brain.

The primary source of omega-3 PUFAs in the American diet is seafood (Blanchard, 2006). The Food Advisory Committee of the F.D.A. has issued a warning for pregnant women to limit their consumption of fish to reduce their risk of methyl mercury (MeHg) exposure (Hibbeln et al. 2007). This has consequently led to decreased intake of PUFAs among pregnant women (Hibbeln et al. 2007).
The first few months after birth are still part of the critical growth period of the brain, and infants still require a steady supply of PUFAs in their diet. Breast milk concentrations of DHA have been found to be proportionate to the maternal consumption of DHA (Jensen, Maude, Anderson, & Heird, 2000). Therefore it is important for breastfeeding mothers to continue to ingest adequate PUFAs (Jensen et al., 2000). Infant PUFA status in breastfed babies has been associated with maternal PUFA status (Jensen et al., 2000). In this paper the author will explore the evidence for the importance of adequate PUFA intake during gestation and lactation and its subsequent effect on the neural and cognitive development of infants.

**Infant Cognitive Development**

**Timeframe of Development**

The human brain begins to develop during the early weeks in utero and continues to develop even after birth. Formation of the central nervous system begins by week four of gestation when the spinal cord and two brain lobes begin development (Brown et al., 2008). During the latter half of pregnancy, brain cells are no longer developing rapidly but are building their lipid and protein stores, especially during the last five weeks of gestation (Brown et al., 2008). There must be enough DHA during these times of critical growth for optimal performance and function of the central nervous system (Brown et al., 2008). Many organ systems’ cells differentiate completely in utero, but the brain completes differentiation after birth to become fully functional (Saladin, 2007). Myelination of the nervous system continues through childhood and is competed in adolescence (Saladin, 2007).

**Assessment Methods**

*Bayley Scales of Infant Development.* The Bailey Scale of Infant Development (BSID) is used as a measure of infants’ and young children’s general development (Eilander et al., 2007).
BSID is the most common tool for assessing cognitive and motor development in infants (Jacobson et al., 2008). It has been standardized on a very large population and is quite technical (Eilander et al., 2007). BSID is considered to be a relatively poor predictor of intelligence later in life, though comparatively it is easier to perform than other more precise methods (Eilander et al., 2007). Two frequently used subtests of the BSID are the Mental Development Index (MDI) and the Psychomotor Development Index (PDI) (Eilander et al., 2007).

**Kaufman Assessment Battery for Children -II.** The Kaufman Assessment Battery for Children II (KABC-II) is a test designed to measure intelligence and achievement in children aged 2.5 to 18 years old (Mays, 2009). It assesses four realms of intelligence: sequential processing, simultaneous processing, mental processing, and nonverbal abilities (Dececi & Koletzko, 2005). The sequential processing section evaluates the child’s ability to arrange stimuli in a sequential order, such as numbers or word order, to solve problems (Helland et al., 2008). The simultaneous processing scale requires the child to process many stimuli at once to solve spatial, analogical, and organizational problems (Helland et al., 2003). Face recognition is a commonly used evaluation for simultaneous processing (Helland et al., 2008). The mental processing composite of the KABC-II consists of the sequential and simultaneous processing components and is meant to assess the child’s style of problem solving and information processing (Helland et al., 2003). The nonverbal portion is assessed using subtests of the sequential and simultaneous processing sections that do not require words; the examiner uses gestures to give instruction while the child responds with movements (Helland et al., 2008). The raw scores of these four elements are standardized to have a mean of 100 with a standard deviation of 15 (Helland et al., 2003).
Other Methods of Assessment. Many other assessment methods are available to evaluate either specific components of mental development or development at specific time frames. The Gesell Developmental Inventory (GDI) is used to assess an infant’s gross motor development (Eilander et al., 2007). Language development can be measured using the Clinical Linguistic and Auditory Milestone Scale (CLAMS) (Eilander et al., 2007). The Peabody Picture Vocabulary Test (PPVT) evaluates receptive vocabulary and scores are correlated with verbal and full scale intelligence scores of the Wechsler Intelligence Scale for Children-III (Oken et al., 2008). Visual-motor problem solving development can be evaluated with the Clinical Adaptive Test (Eilander et al., 2007). Another assessment of visual-motor development is the Wide Range Assessment of Visual Motor Abilities (WRAVMA) that looks at the three domains of visual-spatial (matching), visual motor (drawing), and fine-motor skills (a pegboard test) (Oken et al., 2008). The McCarthy Scales for Children’s Abilities (MCSA) can be used to evaluated general neurodevelopment through five subscales: perceptive-performance, memory, verbal, quantitative, and motor (Martinez et al., 2008). The Fagan Test of Infant Intelligence (FTII) uses a series of photos shown to an infant to test pre-explicit recognition memory which is a predictor of declarative memory abilities in the medial temporal cortex later in life (Jacobson et al., 2008).

Polyunsaturated Fatty Acids

Definition

A large portion of human brain tissue is lipids and specifically fatty acids. The lengths of fatty acids can range from “short chain fatty acids” to “very long chain fatty acids” as categorized by the number of carbons bound together in the chain (Gropper, Smith, & Groff,
2009). The lengths vary from four to about 24 carbons (Gropper, Smith, & Groff, 2009). The term PUFA is used when there is two or more double bonds between carbons in the chain (Gropper, Smith, & Groff, 2009). This structure is considered unsaturated because only one hydrogen can bind to a carbon at a double bond; comparatively each carbon is bound to two hydrogen atoms in a saturated fat (Gropper, Smith, & Groff, 2009). Figure 1 illustrates the structural difference between an unsaturated fat and a saturated fat. The PUFAs that are nutritionally important may have as many as six double bonds (Gropper, Smith, & Groff, 2009). A bend in the chain occurs at locations of double bonds (Gropper, Smith, & Groff, 2009). It is this unsaturated structure and kinked formation of double bonds that allows for fluidity of cell membranes (Gropper, Smith, & Groff, 2009).

**Essential Fatty Acids.** The human body is capable of synthesizing some fatty acids, but there are two it is not able to produce (Gropper, Smith, & Groff, 2009). These essential fatty acids are linoleic acid—an omega-6 PUFA—and alpha linolenic acid—an omega-3 PUFA—and both must be supplied through the diet (Gropper, Smith, & Groff, 2009). The body produces enzymes that elongate and desaturate the essential fatty acids by adding carbon atoms to create new fatty acids such as DHA, eicosapentaenoic acid (EPA), and arachidonic acid (AA) (Gropper, 2009).
Smith, & Groff, 2009). These very long chain successors of essential fatty acids are critical for neurological development in humans (Helland et al., 2003). While newborn infants possess the enzymes necessary for elongation and desaturation, the process may not be sufficient (Gropper, Smith, & Groff, 2009). It is estimated that 20g of alpha linolenic acid are needed to produce only 1g EPA (Schuchardt et al., 2009), so infants still need an external source (Gropper, Smith, & Groff, 2009). Linoleic acid, alpha linolenic, acid and their derivatives are all present in human breast milk in varying amounts (Helland et al., 2003).

**Omega-3 to Omega-6 Ratio.** The inefficiency of alpha linolenic acid conversion to DHA is furthered by competition for desaturases. The enzyme in humans that desaturates linoleic acid to produce AA is also used to desaturate alpha linolenic acid (Simopoulos & Cleland, 2003). These essential fatty acids must compete for use of this enzyme to produce their long chain PUFA derivatives (Simopoulos & Cleland, 2003). When the intake ratio of omega-6 to omega-3 fatty acids is too disproportionate, conversion is compromised for the fatty acid that is consumed least (Simopoulos & Cleland, 2003). The average ratio of omega-6 to omega-3 consumption in the U.S. is anywhere from 9:1 to 16:7:1 (Brown et al., 2008; Simopoulos & Cleland, 2003). Omega-6 PUFAs dominate the enzyme needed to desaturate omega-3 PUFAs in this case and omega-3 long chain PUFA status is compromised.

**Function**

Lipids and specifically PUFAs have many functions within the human body. The major role of lipids is to store energy within adipose tissue of the body (Saladin, 2007). These adipose stores also provide insulation and protection for vital organs (Saladin, 2007). Fatty acids are a type of lipid and are structurally important for cell membranes. When DHA and EPA are consumed, they compete with AA for space in cell membranes (Simopoulos & Cleland, 2003).
DHA is present in large amounts in the central nervous system, especially the grey matter of the brain (Brown, 2008). Omega-3 deficiency has been found to decrease cognition in rats, and in developing rodent brains, DHA depletion has resulted in decreased hippocampal soma size and decreased synaptic vesicles (Cao et al., 2009). Conversely, DHA provided during gestation and lactation in rats has been shown to increase density of dendritic spines in the hippocampus and increase the number of some synaptic proteins (Cao et al., 2009). Research such as this has helped to gain a better understanding of how the human brain works.

Food Sources

While the essential fatty acids are present in many foods, the typical American diet provides a high intake of omega-6 fatty acids and significantly less of omega-3 (Simopoulos & Cleland, 2003). Linoleic acid is present in most vegetable oils and meat, in addition to human breast milk, and the body typically stores it in high amounts in adipose tissue (Brown et al., 2008). Alpha linolenic acid can be found in flaxseed, walnuts, soybean oil, canola oil, and leafy green vegetables (Brown et al., 2008). The long chain derivatives of alpha linolenic acid are found primarily in fish and other seafood; fatty, cold water fish generally are the richest sources of DHA and EPA (Brown et al., 2008). Sardines, mackerel, Atlantic salmon, and lake trout are all excellent sources and DHA and EPA, and in a 3.5 oz serving they contain 3.3 g, 2.6 g, 2.2 g, and 2.0g, respectively (Brown et al., 2008). Non-seafood sources of these long chain PUFAs are egg yolks, with 0.4 g per yolk, fortified eggs, with 0.2 g per egg, and microalgae (Brown et al., 2008). Sources of EPA and DHA are shown in table 1.
Table 1. Sources of omega-3 fatty acids

<table>
<thead>
<tr>
<th>Fish &amp; Seafood</th>
<th>Grams</th>
<th>Portion Size</th>
<th>Fish &amp; Seafood</th>
<th>Grams</th>
<th>Portion Size</th>
<th>Fish &amp; Seafood</th>
<th>Grams</th>
<th>Portion Size</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>EPA + DHA</td>
<td></td>
<td></td>
<td>EPA + DHA</td>
<td></td>
<td></td>
<td>EPA + DHA</td>
</tr>
<tr>
<td>Sardines in oil*</td>
<td>3.5oz</td>
<td>3.3</td>
<td>Trout, Rainbow*</td>
<td>3.5oz</td>
<td>1.0</td>
<td>Pike, Walleye*</td>
<td>3.5oz</td>
<td>0.3</td>
</tr>
<tr>
<td>Mackerel</td>
<td>3.5oz</td>
<td>2.6</td>
<td>Bass, Striped</td>
<td>3.5oz</td>
<td>0.8</td>
<td>Catfish, Wild*</td>
<td>3.5oz</td>
<td>0.2</td>
</tr>
<tr>
<td>Salmon, Atlantic,</td>
<td>3.5oz</td>
<td>2.2</td>
<td>Oysters*</td>
<td>3.5oz</td>
<td>0.6</td>
<td>Fish Sticks</td>
<td>3.5oz</td>
<td>0.2</td>
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<tr>
<td>Farmed*</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Lake Trout*</td>
<td>3.5oz</td>
<td>2.0</td>
<td>Catfish*</td>
<td>3.5oz</td>
<td>0.5</td>
<td>Haddock*</td>
<td>3.5oz</td>
<td>0.2</td>
</tr>
<tr>
<td>Herring*</td>
<td>3.5oz</td>
<td>1.8</td>
<td>Pollock*</td>
<td>3.5oz</td>
<td>0.5</td>
<td>Lobster*</td>
<td>3.5oz</td>
<td>0.2</td>
</tr>
<tr>
<td>Salmon, Sockeye*</td>
<td>3.5oz</td>
<td>1.5</td>
<td>Shrimp*</td>
<td>3.5oz</td>
<td>0.5</td>
<td>Perch, Ocean*</td>
<td>3.5oz</td>
<td>0.2</td>
</tr>
<tr>
<td>White Fish, Lake*</td>
<td>3.5oz</td>
<td>1.4</td>
<td>Tuna, White, Canned</td>
<td>3.5oz</td>
<td>1.7</td>
<td>Salmon, Red*</td>
<td>3.5oz</td>
<td>0.2</td>
</tr>
<tr>
<td>Anchovies*</td>
<td>3.5oz</td>
<td>1.4</td>
<td>Swordfish</td>
<td>3.5oz</td>
<td>0.8</td>
<td>Snapper, Red*</td>
<td>3.5oz</td>
<td>0.2</td>
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<td></td>
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</tr>
<tr>
<td>Salmon, Chinook*</td>
<td>3.5oz</td>
<td>1.2</td>
<td>Flounder*</td>
<td>3.5oz</td>
<td>0.5</td>
<td>Clams*</td>
<td>3.5oz</td>
<td>0.2</td>
</tr>
<tr>
<td>Bluefish</td>
<td>3.5oz</td>
<td>1.2</td>
<td>Scallops*</td>
<td>3.5oz</td>
<td>0.5</td>
<td>Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halibut*</td>
<td>3.5oz</td>
<td>1.1</td>
<td>Carp</td>
<td>3.5oz</td>
<td>0.3</td>
<td>Egg Yolk*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oysters</td>
<td>3.5oz</td>
<td>1.0</td>
<td>Cod*</td>
<td>3.5oz</td>
<td>0.3</td>
<td>DHA</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Fortified Egg*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmon, Pink*</td>
<td>3.5oz</td>
<td>1.0</td>
<td>Crab</td>
<td>3.5oz</td>
<td>0.3</td>
<td>Human Milk*</td>
<td>3.5oz</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*mercury content <0.1ppm
(adapted from Brown et al., 2008).

Maternal Intake of PUFA and the Effect on Infant Development

Mother’s Intake

Maternal Lipid Status. A pregnant woman’s body needs different amounts and types of lipids for various purposes during gestation. During the first half of pregnancy a woman’s body builds up fat stores to be used as energy later (Brown et al., 2008). Blood lipoprotein levels elevate when fat mobilization increases in the second half of pregnancy (Brown et al., 2008). It is
during this time that triglyceride levels increase most dramatically to three times the pre-pregnancy levels (Brown et al., 2008).

Changes in Intake and Need during Pregnancy and Lactation. It is generally estimated that pregnant women need about 300 mg of EPA and DHA per day and the Food and Drug Administration advises against consuming more than 2 g per day (Brown et al., 2008). Fish and seafood are the best source of EPA and DHA but also have the potential to expose the mother and fetus to methyl mercury (Brown et al., 2008). Pregnant women are advised to consume no more than 12 oz of low mercury fish per week that are recognized as good sources of these two long chain PUFAs (Brown et al., 2008). Older, larger fish typically have higher MeHg levels because they have had more time to accumulate mercury in their tissues (U. S. Food and Drug Administration [F.D.A.] & U.S. Environmental Protection Agency, 2004). Women are advised to avoid consuming swordfish, king mackerel, shark, and tile fish during pregnancy for this reason (F.D.A. & U.S. Environmental Protection Agency, 2004).

Effect on Pregnancy Outcome. Adequate EPA and DHA consumption during pregnancy has been found to lower the risk for delivering a preterm infant (Brown et al., 2008). Sufficient levels even increase the length of gestation by an average of four days (Brown et al., 2008).

Infant’s Supply of PUFA

Umbilical. While in utero, the fetus receives its nourishment from the mother’s blood supply through the umbilical cord and placenta. Placental development begins at about 11 days after conception (Saladin, 2007). The placenta begins providing nutrition to the fetus around week nine and is the only method of nutrient delivery from week 12 until birth (Saladin, 2007). The placenta’s nutrient requirements are met before the fetus’ when supply is limited; therefore pregnant mothers need to consume adequate nutrient amounts and be conscious of their intake
(Brown et al., 2008). Nutrient transfer across the placenta depends on the size and charge of molecules, lipid solubility, and concentration in the maternal and fetal blood (Brown et al., 2008). Though much is still unknown about the transfer of long chain PUFAs across the placenta, placental proteins such as fatty acid transport protein (FATP) and placental plasma membrane fatty acid binding protein (p-FABPpm) are thought to be involved (Peng et al., 2009). There has been shown to be a significantly higher proportion of long chain PUFAs in fetal blood than maternal; this suggests that the placenta may preferentially transfer long chain PUFAs to the fetus (Cetin & Koletzko, 2008). After birth the infant’s supply of nutrients is still dependent upon maternal consumption in breastfed infants.

*Breast Milk.* The nutrient composition of a woman’s breast milk is generally proportionate to her dietary intake. Studies have found that both short term diet and habitual intakes influence breast milk composition of long chain PUFAs (Peng et al., 2009). One study reported a doubling of DHA content and a seven fold increase of EPA in breast milk when mothers were supplemented with 6g fish oil per day for only 3 weeks (Jensen et al., 200). However, it is estimated that at least 1g DHA must be consumed by the mother in order to achieve a DHA breast milk content of 1% wt (Cetin & Koletzko, 2008). While women may need to consume high levels of DHA during lactation to attain an appropriate milk composition, studies have consistently shown a dose response relationship between maternal intake and the content of the mother’s milk (Makrides, 2008). This means that a woman can influence the levels of PUFAs in her breast milk available to her infant directly through her diet.

**PUFA and Cognitive Development**

Many studies have been conducted to examine the relationship between maternal omega-3 PUFA or DHA intake and the effect on infant brain development. Researchers have looked at
intake during different times of development and primarily during gestation, lactation, and even PUFA supplementation of the infant after birth. This relationship has been studied through observational and experimental settings and findings have been somewhat inconsistent from study to study.

Studies of Observational Maternal Intake. Research has been done to better understand what pregnant women are eating and the effect it is having on their infants. Oken et al. (2008) conducted a study to look at what the benefits and risks of maternal fish intake were on the infant’s cognitive development (Oken et al., 2008). In this prospective pre-birth cohort study researchers gave mothers a semi-quantitative food frequency questionnaire (FFQ) during their second trimester of pregnancy. They also took hair and blood samples from some women to determine their mercury levels. With the results of the FFQ, they evaluated maternal EPA and DHA intake using food nutrient databases and validated results with maternal erythrocyte EPA and DHA levels. The mean maternal fish intake was 1.5 servings per week with 14% never consuming fish and 12% eating more than two weekly servings; a serving was generally defined as 3-5oz. The mean EPA and DHA intake from fish sources was 128mg/day and from all sources was 149mg/day. Hair and erythrocyte mercury levels correlated with fish intake. These women’s children were tested at three years of age to determine mental development; receptive vocabulary and visual/motor development were measured using the PPVT and WRAVMA tests (Oken et al., 2008).

Findings of the study done by Oken et al. (2008) were that a maternal fish intake of more than two weekly servings was directly associated with a higher child WRAVMA drawing and total score when compared to children of mothers who did not consume any fish (Oken et al., 2008). As shown in Figure 2, when adjustments for mercury levels were made, generally positive
Figure 2. Associations of maternal fish intake (>2 weekly servings vs. never) and erythrocyte mercury levels (top decile vs. below) with child cognitive test results at age 3 years (adapted from Oken et al., 2008).

Fish associations were found with all the test scores among children whose mothers ate more than two servings per week. However, there was no evidence for an advantage of less than two weekly servings of fish when compared to no fish. Children of the 8% of mothers who consumed two or more servings of canned tuna per week had higher PPVT and WRAVMA total scores compared to the children of mothers who never ate canned tuna. The study found that on average for each 100mg of EPA and DHA the mother consumed from fish, the child would have a PPVT score that was 0.5 points higher and a WRAVMA score 1.1 points higher; however, EPA and DHA from all sources and maternal erythrocyte levels were not associated with child scores. Higher maternal mercury levels had an association with lower child test scores; the strongest associations seen were among the PPVT, WRAVMA drawing, and WRAVMA total scores. When maternal fish intake and mercury levels were examined simultaneously, children of women below the top decile for mercury content and who consumed more than two weekly servings had higher WRAVMA total scores as compared to children whose mothers consumed no fish. Even children whose mothers were in the top decile for mercury content but consumed more than two weekly servings had somewhat higher WRAVAM scores. Alternatively children of women in the top
decile for mercury content who consumed two or less servings of fish per week had somewhat lower WRAVMA scores (Oken et al., 2008).

The FFQ was administered during pregnancy which makes the reported maternal fish intakes more reliable than if it was given after birth (Oken et al., 2008). Unfortunately the study had a fair number of weaknesses. A disadvantage of this study was that many of the children included were breastfed which could potentially play a role in cognitive development and therefore may affect the strength of the findings in this study. The researchers collected hair samples from only a small group of women and never assessed the children’s erythrocyte mercury levels. They also never looked at other potential contaminants in fish besides mercury (Oken et al., 2008).

In a second study, conducted by Hibbeln et al. (2007), researchers looked at whether the United States’ recommendations for gestational fish intake protected against adverse neurodevelopmental outcomes (Hibbeln et al., 2007). In this observational cohort, 11,875 pregnant women living in Bristol, U.K. were given a FFQ at 32 weeks gestation. The researchers categorized women as consuming either no fish (12% of the women), some fish (1-340g fish per week and 65% of the women), or more than 340g fish per week (23% of the women). The calculated fatty acid values of the seafood reported in the FFQ were based on characteristics of typical British seafood as categorized by white fish, oily fish, and shellfish. In order to validate the self reported intake data, researchers used two tests of biomarkers in a sample of the women. First, maternal erythrocyte DHA content positively correlated with reported oily fish consumption (P<0.0001), and second, umbilical cord methyl mercury content positively associated with reported levels of fish consumption. Researchers measured continuous development of the infants by questionnaires that were mailed to the homes for the mothers to
complete. They were mailed when the children were 6, 18, 30, and 42 months old and looked at four domains of development: gross motor, fine motor, communication, and social skills. A representative subpopulation of the cohort (1045 children) was tested at 18 months of age by a trained psychologist in a controlled setting. The results of the test administered on the study site positively correlated with the reported answers from the mothers (P<0.0001). All of the children’s IQ levels were tested when they were 8 years old using a portion of the WISC-III through standard neuropsychological testing procedures at the study research clinic (Hibbeln et al., 2007).

Results of the study done by Hibbeln et al. (2007) showed no adverse effect of a maternal consumption of more than 340g per week of seafood (Hibbeln et al., 2007). The unadjusted data consistently showed no worse outcomes for children of women who consumed more than 340g of weekly seafood as compared to children of women who consumed no seafood. Contrarily the unadjusted data showed a greater risk for suboptimum scores among children of mothers who did not consume any seafood. Scores for children of women who consumed some seafood showed a risk for suboptimum development between those of mothers who consumed no seafood and those who consumed more than 340g, implying a dose-response relationship. Higher maternal omega-3 intake was associated with a lower risk of suboptimum verbal IQ scores and both the unadjusted and adjusted data showed similar protective effects for all the outcome scores, some of which are shown in Figure 3. Researchers also looked at 14 specific nutrients in which deficiencies could have the potential to stunt verbal development. In comparing children of mothers who consume no seafood and mothers who consume more than 340g they found an even greater risk for low verbal IQ scores among children of women that consume no seafood. The researchers commented that these results implied the possibility of an underestimation for the
risks of consuming no seafood; however, they chose to still focus on food categories because it required less estimation of food nutrient profiles. Only 1.7% of the women in this study took fish oil supplements during pregnancy and while the researchers did not do as detailed an analysis as for seafood consumption, children of these women who did not eat fish scored similarly to children of women who ate fish. The data showed no benefit in any of the outcome measures of maternal seafood consumption at less that 340g per week, the recommended amount for pregnant women in the U.S. (Hibbeln et al., 2007).

Hibbeln et al. (2007) conducted a very strong and thorough study (Hibbeln et al., 2007). While many of the measures in this study were dependent on self reported data, which are always subject to potential biases, the researchers attempted to account for and correct many areas that would skew the results. They adjusted for 12 individual categorical covariates such as maternal education level,
breastfeeding, and stressful life events during gestation (Hibbeln et al., 2007). The researchers were dedicated to validating results of self reported data through the use of alternative tests on samples of the cohort. In regards to the original research question of this study, the use of a British sample group was likely to have represented an even higher methyl mercury intake than is common in the U.S. and higher than the values the U.S. recommendations are based on (Hibbeln et al., 2007). British seafood generally has a higher methyl mercury content and the British population has an average overall methyl mercury intake of 0.05µg/kg body weight as compared to the average U.S. intake of 0.02µg/kg body weight (Hibbeln et al., 2007). Therefore it is a reasonable assumption to expect children in the U.K. to be at a greater risk for poor mental development because of methyl mercury exposure when compared to children in the U.S. One weakness of this study however is that the FFQ used only had three questions that directly asked about seafood consumption (Hibbeln et al., 2007).

In another study conducted by Mendez et al. (2008) researchers examined the relationship between seafood consumption during pregnancy and the child’s scores on cognitive tests at 4 years old (Mendez et al., 2008). This cohort study took place on the Spanish island of Menorca where seafood consumption is relatively common. The study subjects were recruited while they were pregnant; however, interviewer administered FFQs on usual intake during pregnancy were not given until 3 months after they gave birth. The 42 item semi-quantitative FFQ had questions on fish, squid/octopus, and shellfish consumption. The researchers categorized the women’s weekly fish consumption as none (3.3%), ≤1 serving (49.2%), >1-2 servings (32.9%), >2-3 servings (12.8%), and >3 servings (5.1%). Fish accounted for 57.7% of the total seafood intake; researchers looked at squid and shellfish intake separately from fish because on average they contain lower amounts of DHA than fish. When the children were 4
years of age, their neurodevelopment was assessed using the MCSA and results were stratified by breastfeeding duration (Mendez et al., 2008).

Mendez et al. (2008) found that scores were highest among children whose mothers reported consuming fish >2-3 times per week (Mendez et al., 2008). The children of mothers who had ≥3 weekly servings of fish had average scores similar to the children of women who reported ≤1 weekly servings of fish. The only association between fish consumption and higher test scores was among children who were breastfed <6 months. Among children breastfed <6 months, an average increase of 5.9 to 8.6 was seen in scores of all subscales (except the motor skills subset) for fish intake of >2-3 times per week as compared to ≤1 time per week. However children breastfed for ≥6 months had higher mean scores overall. These children’s scores though were neither strongly nor consistently associated with maternal fish intake. When the researchers looked at other seafood besides fish, consumption was associated with lower general cognitive, perceptual-performance, verbal, and numeric scores, regardless of breastfeeding duration. These contrasting data for fish versus other seafood intakes resulted in no association between overall seafood intake and child neurodevelopmental test scores (Mendez et al., 2008).

This study had numerous strengths. The researchers were aware of many potential confounders and attempted to adjust for them. Their stratification of results by breastfeeding duration improved the strength of their findings. They also compared data with supplementary statistical analysis that found similar results when breastfed children were excluded all together. The researchers considered the potential of seafood contaminants to affect neurodevelopment and looked at cord blood levels of DDT, DDE, and polychlorinated biphenyls (Mendez et al., 2008). While none of these compounds were found to confound the associations and therefore were omitted from the final analysis, it is an example of the diligence in this study. Unfortunately
the report of the study failed to mention some potentially important details, such as the procedure by which the children were tested. It also did not include whether or not the researchers actually evaluated the EPA and DHA levels of the foods reported in the FFQ. The relatively small sample size of 392 women and the fact that the FFQ was administered 3 months after birth raises some questions as to the strength of this study’s findings; however, these researchers considered details omitted from other studies and the results are still valuable.

In the last observational study to be reviewed in this paper Jacobson et al. (2008) conducted a prospective longitudinal study of a cohort of Inuit infants in Arctic Quebec to examine the relationship between cord plasma phospholipid concentrations of DHA and neurodevelopmental outcomes (Jacobson et al., 2008). In this study they gathered a sample of 109 Inuit pregnant mothers to form their sample. The three largest Inuit villages in the Hudson Bay were represented within the sample, all of which consume fish and sea mammals as staples in their native diets. Researchers conducted interviews with the mothers at mid pregnancy and 1 month after birth to attain information of lifestyle and demographic characteristics, though they never used any assessment of maternal food intake. In order to evaluate long chain PUFA status, researchers obtained a 30mL umbilical cord blood sample at birth, a 12.5mL maternal blood sample at delivery, and a 10mL breast milk sample from breastfeeding mothers at 1 month postpartum. Cord concentration levels of DHA were divided into quartiles in order to construct groups of prenatal DHA consumption. The mean milk DHA concentration was found to be 0.6% of total fatty acids, considerably higher than the mean 0.2% among Caucasian women in the Vancouver area. The mean cord concentration of 3.7% was also higher than the reported mean of 1.2% among women in Southern Quebec. At 6 months of age infants were assessed using the
FTII and then again at 11 months using the FTII and the mental and psychomotor indices of the BSID-II (Jacobson et al., 2008).

Jacobson et al. (2008) found maternal and cord plasma phospholipid DHA concentrations to be strongly related, and the correlation between DHA to AA ratio in maternal and cord plasma was even stronger (P < 0.001) (Jacobson et al., 2008). The mean cord plasma concentration of DHA was significantly higher than maternal concentration. The researchers observed a beneficial association between higher cord DHA and the DHA to AA ratio with FTII scores at 6 months of age as well as scores on the BSID-II at 11 months. These beneficial effects were generally seen as a dose-response relationship. However, only the two highest prenatal intake groups showed an effect on the psychomotor index of the BSID-II (Jacobson et al., 2008).

There were many unique qualities to this study. This was a rare study that chose to assess maternal intake levels based solely on biomarkers (Jacobson et al., 2008). Also, choosing a relatively homogenous sample group that had dietary PUFA intake in common reduced the need to assess dietary characteristics through traditional assessment methods such as FFQ. This Inuit population also had a high adoption rate in common and 9.2% of the infants in this sample were adopted. While this could potentially skew the study results, researchers controlled for this along with 16 other covariates. Perhaps the researchers could have found stronger or even more associations if they had a larger sample group to study. The report of this study was somewhat vague in its details of methodology and results, which also retracted from the overall strength of this study.

Oken et al. (2008) found that pregnant women benefited from consuming fish more than two times per week (Oken et al., 2008). Their observation that children of women who had high mercury levels and a high weekly fish intake had higher scores than children of mothers who ate
the recommended fish intake (less than two weekly servings) is extremely significant. This
association brings to light the suggestion that perhaps high intakes of DHA could work to
decrease or override the negative effects of a high mercury exposure from fish. Hibbelen et al.
(2008) also found no negative effects of a higher rate of fish consumption among pregnant
women (Hibbelen et al., 2008). Children of women who did not consume fish had more risk for
lower neurodevelopmental scores in both studies. While Mendez et al. (2008) found no
association between total seafood intake and infant mental development, they did see a positive
association between fish intake and development when they separated types of seafood (Mendez
et al., 2008). Their study was the only one to look at forms of seafood and DHA sources
separately, and their results for the individual types of seafood could help to guide research
towards which DHA sources should be recommended to pregnant women. The last study
reviewed was unique in its method of assessing maternal DHA status. Jacobson et al.’s (2008)
study most strongly suggested association through a dose-response relationship (Jacobson et al.,
2008). They observed a positive correlation between maternal DHA status and infant mental
development but only in women with the highest DHA levels. This study also found a positive
relationship with infant development at a much younger age than the other studies. While all four
of these studies had positive findings, the variations among them suggests there is still a need for
a better understanding of the specific details of the relationship between maternal DHA intake
and infant development.

Studies of Experimental Maternal Intake. Researchers have been able to manipulate the
PUFA intake by pregnant women through experimental and interventional studies. Through this
method of study they have gained a better understanding of the role maternal PUFA intake can
play in the mental development of infants. Helland et al. (2003) conducted one such
experimental study in Norway to test their hypothesis that the fetus and newborn infant would benefit from an increase in the maternal intake of long chain PUFAs during pregnancy and lactation (Helland et al., 2003). They began with an initial sample of 341 pregnant mothers whom they randomly assigned to take either 10mL of cod liver oil or 10mL of corn oil per day in a double blind setting. The cod liver oil contained 1,183mg of DHA and 803mg of EPA in each dose and the corn oil contained 4,747mg linoleic acid and 92mg alpha linolenic acid per dose. The two supplemental oils had equal fat soluble vitamin compositions. Supplementation of these two groups began at 18 weeks gestation and continued through 3 months after giving birth. The women completed self administered FFQs at the beginning of the study (18 weeks gestation) and at 35 weeks gestation. Responses to the FFQs showed no differences in nutrient intake between the two study groups at 18 weeks gestation but there were significant differences in linoleic acid, AA, EPA, and DHA intakes after 35 weeks gestation consistent with the supplementation. Umbilical cord blood samples and infant blood samples were taken at age 4 weeks and 3 months. Breast milk samples were also taken at 4 weeks and 3 months after birth. When the children were 3 months old their mothers filled out questionnaires about the infant's usual diet concerning breast feeding and supplemental cod liver oil. This was of particular concern to the researchers because the Norwegian guidelines for infant nutrition recommend that 5mL of cod liver oil be given to infants daily beginning at 4 weeks of age. The researchers invited 135 children to return at 4 years old to take the K-BAC assessment of intelligence and the final sample tested was 84 children (Helland et al., 2003).

Helland et al. (2003) found that children in the maternal cod liver oil group scored significantly higher on the Mental Processing Composite of the K-BAC at 4 years old as compared to children of the maternal corn oil group (Helland et al., 2003). Scores for this subtest
correlated significantly with maternal intake of EPA and DHA during pregnancy. While researchers observed a tendency toward higher scores among these same children on the Sequential Processing scale, Simultaneous Processing scale, and Nonverbal scale, the results were not significant. The 35 children whose mothers reported as taking cod liver oil supplements showed no differences in scores when compared to children not being supplemented. Researchers found no correlation between umbilical plasma phospholipid concentrations of long chain PUFAs and test scores; however, a correlation was observed between plasma phospholipid concentrations of DHA and intelligence scores. Helland et al. (2003) concluded that higher maternal DHA intake resulted in an increased transfer to the fetus and figured infants of the cod liver oil group received on average about 2.7-fold more DHA than children of the corn oil group (Helland et al., 2003).

In a second follow up of this study, Helland et al. (2008) measured intelligence in 143 children from the original study when they were 7 years old using the same K-BAC test (Helland et al., 2008). The researchers again evaluated the children’s supplementation of cod liver oil during preschool. They found that from the original maternal cod liver oil group, 44 of the children they tested took cod liver oil supplements regularly, 22 had taken it sporadically, and 16 never received cod liver oil supplementations. In the maternal corn oil group 28 of the children regularly received cod liver oil supplements, 14 received sporadic supplementation, and 19 had not taken any. The researchers found no statistically significant difference in scores at 7 years old between the two groups. While there was a tendency toward higher sequential processing scores in the maternal cod liver oil group, the results were not significant. The levels of long chain omega-3 PUFAs in maternal and neonatal blood samples positively correlated with sequential processing scores. Maternal plasma phospholipid levels of DHA and alpha linolenic acid
positively associated with scores on the sequential processing scale at 7 years old (Helland et al., 2008).

The researchers in these two studies conducted a thorough cohort to examine the relationship between maternal PUFA intake and its effect on the mental development of the child. It was an advantage that they assessed the children’s intelligence level in at 4 and 7 years old. Especially considering the slight differences in results they found between the 4 year old scores and the 7 year old scores. Not many other studies have looked at the intelligence level in childhood when examining the effect of maternal PUFA intake; this allowed for a better comparison to PUFAs affect on early development and a better understanding of what kind of long term effects PUFAs may have on mental development. The initial sample size of women was relatively small and unfortunately the samples of children they tested at 4 and 7 years old were even smaller. A unique characteristic of this study was the Norwegian nutritional guidelines to supplement infants with 5mL cod liver oil (Helland et al., 2003). The researchers measured the number of children that were supplemented with cod liver oil in infancy and were able to evaluate its potential effect on cognitive development separately from PUFA supply in gestation or through breast milk.

In a controlled study conducted by Judge, Harel, and Lammi-Keefe (2007) researchers assessed the relationship between a maternal consumption of a high DHA containing food during pregnancy and the problem solving and recognition abilities in the mothers’ infants (Judge et al., 2007). In this double blinded placebo controlled study, 29 pregnant women at less than 20 weeks gestation were recruited and randomly assigned to one of two groups. The experimental group consisted of 14 women who were instructed to consume one DHA containing cereal bar per day that was given to them by the researchers from the start of the study until they gave birth. The
control group (15 women) was also told to eat one cereal bar per day given to them by the researchers from the start of the study until birth. The experimental and placebo cereal bars both contained 1.7g fat, from low EPA fish oil in the experimental bar and from corn oil in the placebo bar, and were identical in fat soluble vitamin content. The DHA bar had 300mg DHA and an EPA to DHA ratio of 1:8 per cereal bar. Women in both groups were told to eat three, five, or seven cereal bars per week and the average cereal bar consumption was five bars per week. The researchers conducted four 24 hour recalls by an interviewer with all of the women during the course of pregnancy. The mean dietary DHA intake did not differ between the two groups at about 99mg DHA per day from recalled food sources, but the women in the DHA cereal bar group had an average combined DHA intake of 313mg from their diets and the fortified cereal bars (Judge et al., 2007).

The researchers in this study evaluated the infants’ cognitive development at 9 months of age through two methods (Judge et al., 2007). First they designed a problem solving test in which they demonstrated a two step problem to the infant, one step at a time, and let the child practice each step. Then they presented the combined the two step process which the infant had to complete in order to retrieve the toy. The process was designed to test the infant’s problem solving capabilities and memory. Each infant was given 5 attempts to complete the complete the puzzle and the process was videotaped to be watched and evaluated by the researchers later. The second assessment method was the FTII. Both of these tests were generally conducted in the infants’ homes and parents were instructed beforehand to minimize any distractions or external stimuli. The assessments were intentionally conducted when the infants were not ill and during whatever time of day they were most active and alert (Judge et al., 2007).
As a result of this study, Judge et al. (2007) found that children of women in the DHA fortified cereal bar group scored higher overall on the toy activity to assess problem solving ability and memory (Judge et al., 2007). The number of times children knocked the puzzle over or off the table, both of which were considered failing, were the same between children in the two groups. The researchers also observed no significant differences in the children's scores on the FTII between the two groups (Judge et al., 2007).

While the researchers' attention to detail throughout this study was consistent, there were changes that could have been made to improve the quality of this study. The sample size of only 29 women may be too small to draw any strong conclusions from. Also considering the four different treatment doses among the sample (DHA bars three times, five times, and seven times per week and the placebo bars) may also mean there were not enough women within the group to really observe strong associations. However, the use of four 24 hour recalls provided fairly comprehensive and most like representative data on usual maternal dietary intake and gave a level of detail above the other studies that have been mentioned in this review. The researchers also obtained data on the use of infant formula containing DHA, formula not containing any DHA, exclusive breast feeding, and combinations of formula and breast feeding as well as durations of each (Judge et al., 2007). The researchers also attempted to provide consistency among the infants' ability to perform the assessments by testing the children at very specific times (Judge et al., 2007).

In the final experimental study to be reviewed, Tofail et al. (2006) tested their hypothesis that fish oil supplementation provided to pregnant women in the third trimester of pregnancy would provide more DHA to the fetus and improve its mental and psychomotor development (Tofail et al., 2006). This study was a follow up to a randomized double blind study of 400
pregnant women in Dhaka, Bangladesh. These women were all recruited in their 25th week of gestation to test the effects of fish oil supplementation verses soy oil supplementation. The randomly assigned experimental group were given 1g fish oil capsules and instructed to take four per day which provided 1.2g DHA and 1.8g EPA daily. The control group received identical soy oil placebo capsules, in doses of 1g, and was also instructed to take four daily. These provided the women with 2.25g linoleic acid and 0.27g alpha linolenic acid per day. Supplementation began in the 25th week of pregnancy when the study was started and ended once the women gave birth. When the infants were 10 months old the researchers tested their mental development using the BSID-II and also assessed their behavior during the assessment. Behavior was assessed based on five components: activity, emotional tone, vocalization, and responsiveness to the examiner within the first 10 minutes, cooperation with the test procedure. Each infant was tested by two researchers and evaluated separately; the researchers evaluations were highly correlated with each other (r>0.92). The researchers also evaluated the women on many different characteristics of socioeconomic status and found the two groups to be similar. The women in each group were also similar in terms of education level, occupation, and whether they breast fed their infant. Lastly the researchers evaluated the quality of the home stimulation in the presence of the mother and the infant (Tofail et al., 2006).

On the whole, Tofail et al. (2006) found no difference in mental or behavioral development in children of women in the two different groups (Tofail et al., 2006). In fact BSID-II scores significantly correlated with the home environment scores and some of the socioeconomic scores. Home environment and birth weight were found to be predictors of the mental development index of the BSID-II while gestational age, home environment, and some socioeconomic status characteristics were predictors of the psychomotor development index. The
researchers concluded that perhaps the timing of initiation of their study and its duration were not sufficient to observe a benefit to the mental development of the infants (Tofail et al., 2006).

This study contained some flaws that perhaps its inconclusiveness could be attributed to. First the researchers never assessed the maternal diets, either through reported intake or biological means, so they were not able to control for other potential sources of DHA. Second the study mentioned that soy oil was very common in the diets of this culture; therefore even women in the fish oil group potentially could have been consuming high levels of soy oil (Tofail et al., 2006). Lastly the researchers had the women cease supplementation after giving birth. This means that they were not able to evaluate the affect fish oil could have had on cognitive development through its supply of DHA to breast milk. The study acknowledged the rapid growth period of the infant brain from the last trimester of pregnancy through the first few months of life. They found that 82% of the women in the sample breastfed their infants (Tofail et al., 2006), so they missed the opportunity to observe any potential effects on infant development that could have taken place after birth when the mother received DHA supplementation.

In contrast to the observational studies, the experimental studies reviewed here had some inconclusive results. A notable and potentially very significant difference between these experimental studies is that Helland et al. (2003; 2008) assessed the children's mental abilities at a much older age than in the other two studies (Helland et al., 2003; Helland et al., 2008). Helland et al. (2003; 2008) found beneficial associations between maternal long chain PUFA supplementation and the infants' mental development at both 4 years and 7 years of age (Helland et al., 2003; Helland et al., 2008). This seems to suggest the possibility that perhaps beneficial effects of maternal PUFA supplementation are not observable in the infant until childhood. Both Judge et al. (2007) and Tofail et al. (2006) assessed the infants' mental development before 1
year old in their samples (Judge et al., 2007; Tofail et al., 2006). Judge et al. (2007) observed beneficial associations on some of the measures of infant development but not all, whereas Tofail et al. (2006) did not witness any relationship between development scores and maternal supplementation (Judge et al., 2007; Tofail et al., 2006). Table 2 shows a summary comparison between these four studies and their findings.

Table 2. Summary of experimental studies of the effect of maternal fish oil supplementation on cognitive development in the infant

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of Study</th>
<th>Treatment</th>
<th>Placebo</th>
<th>DHA content of Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helland et al., 2003</td>
<td>Randomized, double-blind, placebo controlled</td>
<td>10mL cod liver oil daily</td>
<td>10mL corn oil daily</td>
<td>1183mg DHA/day</td>
<td>Significantly higher scores at 4 years of age on the Mental Processing component of the K-BAC in children of women in the cod liver oil group as compared to the corn oil group</td>
</tr>
<tr>
<td>Helland et al., 2008</td>
<td>Randomized, double-blind, placebo controlled</td>
<td>10mL cod liver oil daily</td>
<td>10mL corn oil daily</td>
<td>1183mg DHA/day</td>
<td>Non-significant tendency towards higher sequential processing scores in children of the cod liver oil group; positive correlation between maternal and cord blood DHA levels and sequential processing scores at age 7</td>
</tr>
<tr>
<td>Judge et al., 2007</td>
<td>Randomized, double-blind, placebo controlled</td>
<td>One low EPA fish oil fortified cereal bar per day at 3, 5, or 7 times per week</td>
<td>One corn oil cereal bar per day at 3, 5, or 7 times per week</td>
<td>300mg DHA per bar</td>
<td>Higher overall problem solving and memory scores in children of the treatment group as compared to the control group</td>
</tr>
<tr>
<td>Tofail et al., 2006</td>
<td>Randomized, double-blind, placebo controlled</td>
<td>4-1g fish oil capsules daily</td>
<td>4-1g soy oil capsules daily</td>
<td>1200mg DHA/day</td>
<td>No significant association between fish oil and supplementation and mental development</td>
</tr>
</tbody>
</table>

(Helland et al., 2003; Helland et al., 2008; Judge et al., 2007; Tofail et al., 2006)

Conclusions of Current Studies and Need for Further Research

Results of the eight studies reviewed in this paper have been somewhat inconsistent. The observational studies observed overall positive associations between maternal PUFA intake and
enhanced cognitive development in infants. Alternatively, the experimental studies produced some positive and some inconclusive results. The reasoning for this difference is not blatantly clear. There were varying doses of DHA, the primary PUFA of concern, in all of the studies with low and high doses overlapping among the observational and experimental studies. Generally the studies were conducted well and the analyses were fairly thorough. The most obvious distinction that is consistent in the observational verses experimental studies is that fish or seafood as a whole food was the typical DHA source in the observational studies whereas not one of the experimental studies supplemented women with actual fish. Perhaps there is a more complex nutrient interaction between DHA and the nutrients in whole foods and its overall affect on infant brain development that needs to be studied. A good preliminary study to investigate this further could separate a sample of pregnant women into three study groups: one supplemented with fish, one with fish oil, and one control group given either a placebo food or oil.

As it stands now, with this mix of findings, better understanding is needed of this subject in order to form effective recommendations for pregnant women. The evidence from two of the observational studies (Hibblen et al., 2005; Oken et al., 2008) suggests that the current recommendations given to pregnant women regarding fish and seafood consumption may not be based on the most accurate or thorough information. More research is needed to gain a deeper understanding of the effects of DHA and mercury in fish on the health and wellbeing of both the mother and her child. This more thorough understanding is necessary to provide a more accurate recommendation to pregnant women.

Consequently, none of the studies reviewed in this paper found any negative effects of a moderate to high maternal consumption of DHA and some even observed adverse effects of an inadequate intake. At this time the evidence is pointing towards a benefit of DHA supply during
pregnancy and lactation. Further research is essential for a more conclusive understanding of which variations of timing, amounts, and sources of maternal DHA result in the best outcome for infant mental development.

Resources


