

## **The Effects of Breast Milk Versus Infant Formulae on Cognitive Development**

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### **Abstract**

*Commercially-available infant formulae are designed to provide infants with the same nutritional value as breast milk; however, there are many biological components (i.e., maternally-derived antibodies) that cannot be reproduced. There is evidence in the literature to support the hypothesis that feeding with breast milk provides benefits to the infant in terms of development and cognitive outcome. The most studied components of breast milk are the long-chain polyunsaturated fatty acids, specifically docosahexaenoic acid (DHA) and arachidonic acid (AA). These non-essential fatty acids have been shown to provide a measurable advantage to breast-fed infants over their formula-fed counterparts on childhood scales of cognitive development. Recently, DHA and AA were approved as additives to infant formulae in North America. Breast milk also contains a number of growth factors and hormones that are known to have neural developmental effects, but these effects have not been quantified on behavioural scales. There are also still many more unidentified components of breast milk. Efforts to educate and encourage the feeding of breast milk over infant formulae are underway from the community to international level, with the World Health Organization publishing guidelines on the optimal duration for breastfeeding. It should be noted that there are certain advantages of some formulae over breast milk, most significantly the fact that formulae contain no contaminants (i.e., medications and their metabolites) from the maternal diet.*

Breast milk is considered the gold standard of infant nutrition, with commercially available infant formulae designed to mimic its unique combination of carbohydrates, fat, protein, vitamins and minerals. Breast milk, however, contains numerous components that cannot be manufactured synthetically, including maternally-derived antibodies which protect against disease and infection (Cleary, 2004). Compounding the problem of reproducing breast milk in infant formula is the fact that its exact chemical composition is unknown (Redel & Shulman, 1994; Stehlin, 1996). The World Health Organization recommends that mothers breastfeed exclusively for the first six months and continue to breastfeed, with complementary foods, up to two years of age. Over the last two decades there has been an accumulation of evidence to suggest that infants who receive breast milk may have an advantage over their formula-fed counterparts with respect to cognitive development and I.Q. However, these studies were often poorly designed; they were not always randomized and thus a majority of the comparisons drawn between breast- and formula-fed infants were confounded by genetic and socioeconomic factors. Breast milk and infant formulae may have differential effects on cognitive development for several reasons. Most notable is that factors that promote the development of the central nervous system are either absent from or present in lower (or different) concentrations in infant formulae, including: cholesterol, long chain polyunsaturated fatty acids (LCPUFAs), as well as various growth factors, hormones, vitamins and minerals (Banapurmath, Banapurmath & Kesaree, 1996). This review summarizes available data on the effects of breast milk versus infant formulae on development and cognitive outcome. Each of the aforementioned factors will be examined in turn, drawing from data obtained in both laboratory and clinical settings, in order to provide a comprehensive understanding of current research in the field. Particular emphasis will be placed on the differences in fat content as this has been the focal point of much scientific and commercial interest. At this point it is important to make the distinction between the content of breast milk and the process of breastfeeding as this process itself has been suggested to facilitate mother-infant bonding and in turn influence neurodevelopment (Newton, 1971; Stuart-Macadam, 1995). Recognizing that there also can be advantages to feeding with infant formulae over breast milk, this review also examines the contaminants in breast milk which may negatively impact upon cognitive development of the breast-fed infant.

### **A Comparison of Breast Milk and Infant Formulae**

The nutritional needs of developing infants are not homogenous but depend upon birth weight, gestational age, and growth rate. Similarly, the nutritional

demands of an infant evolve as he/she grows. Breast milk contains nutritional and non-nutritional content that varies over time. The liquid that is produced initially, colostrum, provides proportionally greater amounts of protein and minerals than fat, while this ratio is reversed in the mature milk that is produced later. Breast milk allows for the provision of compounds with developmental and immunoprotective value (see Table 1) which have been putatively linked to the fact that breast-fed infants present with fewer cases of diarrhea (Baker, Taylor & Henderson, 1998; Fuchs, Victora & Martines, 1996; Scariati, Grummer-Strawn & Fein, 1997) gastroenteritis (Abu-Ekteish & Zahraa, 2002), necrotizing enterocolitis (Buescher, 1994; Lucas & Cole, 1990; McGuire & Anthony, 2003; Schanler, Shulman & Lau, 1999), neonatal sepsis (Schanler et al., 1999), and otitis media (Dewey, Heinig & Nommsen-Rivers, 1995; Duncan et al., 1993; Scariati et al., 1997) compared to formula-fed infants.

*Table 1. Basic properties of breast milk and infant formulae with respect to development and immunoprotection.*

<i>Breast milk</i>	<i>Cow's milk-based formulae</i>
non-sterile, variable in content and flavour	sterile, unchanging content and flavour
contains non-essential fatty acids: docosahex aenoic acid (DHA), arachidonic acid (AA)	until recently, contained only essential fatty acids (see below for further discussion)
high in cholesterol factors tht promote development of the nervous system: thyroid stimulating hormone, nerve growth factor	low in cholesterol no human hormones or growth factors
live cells and proteins with immunoprotective function: antibodies, immunoglobulins, lctoferrin, lysozyme, macrophoages, peroxidse	no innate immunoprotective properties
contains vitamins and minerals	contains the same vitamins and minerals, often at higher concentrations due to dereated bio-availability
contains contaminants from maternal dietary intake	no contaminants, unchanging composition

### **Cow's Milk-Based Formulae**

The commercial production of infant formulae is regulated by Health Canada and in the United States by the Food and Drug Administration (FDA). These government agencies are responsible for specifying the nutrients that must be provided. Infant formulae are generally cow's milk-based and vary with regard to calorie, protein, and mineral content. They may be broadly classified as:

1. "Term" formulae are designed for term infants based on the composition of mature breast milk. These formulae provide an average of 68 kcal/100ml energy, 1.5 g/100ml protein (Fewtrell & Lucas, 1999) and are often supplemented with cysteine and taurine as cow's milk contains lower quantities of these amino acids. Taurine, in particular, is involved in the development of the cardiovascular and nervous systems (Michalk et al., 1988) where it plays a role in modulating neurotransmission.
2. "Preterm" formulae are designed for preterm infants and are calorie-enriched to provide 80 kcal/100ml in support of intrauterine nutrient accretion rates (Fairey et al., 1997). These formulae are also supplemented with greater levels of protein and mineral. It has been suggested that the balance between fat and protein content is critical in promoting accretion rates of fat, fat-free mass, and minerals closer to that of a fetus (Fairey et al., 1997).

### **Soy-Based Formulae**

Soy-based formulae were initially developed for infants who exhibited an allergy to cow's milk or lactose intolerance, but now represent over a quarter of commercial sales in the United States (Mendez, Anthony & Arab, 2002). Interestingly, it has been documented that 17-47% of infants also experience a reaction to soy-based ingredients (Wyllie, 1996). These formulae have improved over the years to ensure protein quality and adequate availability of minerals (American Academy of Pediatrics, 1998), such that modern formulations have been demonstrated to support normal growth in term infants within the first year of life (Strom et al., 2001) as well as into adulthood (Mendez et al., 2002). The use of soy flours has been replaced with soy protein isolates. However, there are still concerns over the high phytoestrogenic isoflavone content of soy-based formulae and the possibility of exogenous endocrine effects (Australian College of Paediatrics, 1998; Irvine, Fitzpatrick & Alexander, 1998). Mendez et al.

(2002) conducted a review of all available literature and found a lack of data to support differences in the timing of maturation or sexual development in adolescents and adults who received soy-based formulae in infancy. The authors caution that there is still insufficient evidence from which to draw definite conclusions.

## Fat Content

### Introduction

The requirement for fat in the infant diet has traditionally been considered in terms of energy metabolism. Because infants are only able to ingest a limited amount of fluid per day (Stehlin, 1996), this fluid must provide the maximum amount of nutrients per unit volume. Fat, which yields the greatest number of calories per unit versus carbohydrates or protein, provides the majority of the energy content of breast milk and infant formulae. Breast milk contains animal fats and cholesterol while infant formulae contain vegetable oils such as palm, coconut, corn, soy or safflower oils (Redel et al., 1994). It is now clear that some types of fat may play an important role in the development of the brain and neural networks. Recent interest has focussed on long-chain polyunsaturated fatty acids (LCPUFAs) such as arachidonic acid (AA, 20:4n-6) and docosahexaenoic acid (DHA, 22:6n-3). These fatty acids are found in high proportions in the structural lipids of cell membranes (Martinez, 1992), particularly those of the central nervous system where they constitute nearly 30% of the total fatty acid in grey matter of the brain (O'Brien, Fillerip & Mead, 1964). It should be noted that structural lipids are not available for energy metabolism (Martinez, 1992a). The accretion of DHA and AA occurs during the last trimester of pregnancy (Clandinin et al., 1980; Martinez, 1991), during which they are supplied to the fetus through the placenta (Dutta-Roy, 2000); and in the first year of life (Martinez, 1991; Martinez, 1992b) through the consumption of breast milk which contains a full complement of PUFAs including both precursors and metabolites (Jensen, 1999). Breast milk contains 0.05-0.1% DHA and 0.1%-0.9% AA in North American women (Jensen, 1999). However, it should be noted that these values depend on maternal diet (Innis, 1992; Ruan et al., 1995) and are significantly lower in women who consume very little marine products, such as those who follow strict vegetarian diets (Koo, 2003). In adulthood, the brain has been described to be resistant to altering its fatty acid composition and retains levels of both AA and DHA through insufficiencies of omega-3 and omega-6 fatty acid in the diet (Bourre, Dumont, Piciotti, Pascal & Durand, 1992; Connor, Neuringer & Lin, 1990).

Infant formulae have traditionally only contained the precursor essential fatty acids alpha-linolenic acid (ALA, 18:2n-6; the omega 3 precursor) and linoleic acid (LA, 18:3n-3; the omega 6 precursor) from which formula-fed infants must synthesize their own DHA and AA respectively (Willatts & Forsyth, 2000). While there is evidence that infants can effectively metabolize ALA and LA (Salem, Wegher, Mena & Uauy, 1996), there also is evidence that they do not synthesize these substances at an adequate rate. Lower concentrations of AA and DHA have been detected in the plasma and red blood cell membranes and lower concentrations of DHA have been detected in the cerebral cortex of formula-fed and preterm infants in comparison to breast-fed infants (Farquharson et al., 1995; Makrides, Neumann, Byard, Simmer & Gibson, 1994). The absence of LCPUFAs in infant formulae may be further exacerbated by an inhibition of the incorporation of endogenously produced LCPUFAs by the high concentrations of LA currently present in most formulations. The current hypothesis is that infant formulae containing only the precursors LA and ALA may not be effective in meeting the full nutritional requirements of infants, although various combinations of LA and ALA are still being evaluated and may yet prove effective. This hypothesis has been central to randomized clinical trials of formula feeding in attempts to mimic the beneficial effects of breastfeeding on early development.

In February of 2002, the FDA approved the use of DHA and AA as additives to infant formulae in the United States. Expert panels from the Life Sciences Research Organization assessed nutrient requirements for both term and preterm infant formulas and recommended neither a minimum nor maximum content of either AA or DHA for term infant formulae. For preterm infant formulae, they recommended maximum levels of 0.35% and 0.6% of total fatty acid intake for DHA and AA respectively. While the functional benefits in neural development from infant formulae containing LCPUFA remains controversial, there also exists the potential for excessive and/or imbalanced intake of n-6 and n-3 fatty acids exists with increasing fortification of LCPUFA to infant foods other than liquid formula (Koo, 2003).

### **The Essential Fatty Acids**

Fatty acids are a component of the lipid molecule. There are two essential fatty acids that the body cannot manufacture and must be obtained from dietary intake. The first, alpha-linolenic acid (ALA), belongs to the omega-3 family of fatty acids and can be derived abundantly from flax, and in smaller quantities from canola oil, walnuts, and wheat germ. These foods are not prevalent in the typical North American diet, and as a result

approximately 95-99% of the population of the United States is deficient in this essential fat. This deficiency plays a role in a variety of degenerative diseases including arthritis, heart disease and cancer, diabetic neuropathy, immune function and premenstrual syndrome. The second essential fatty acid, linoleic acid (LA), belongs to the omega-6 family and may be found abundantly in pumpkin, safflower, sunflower, and sesame seeds; corn and soy oils; and, in most species of nut. The typical American diet contains disproportionate amounts of LA in comparison to ALA because of the consumption of large quantities of refined vegetable oils. Examples include margarine, crackers, cookies, and other processed foods. The right ratio of LA acid to ALA in the diet is important and should be maintained around 3:1 or 2:1. Typically, the North American diet offers a ratio of 20:1. There is preliminary evidence to support that an imbalance may lead to a variety of mental disorders, including depression, hyperactivity, and schizophrenia.

### **The Non-Essential Fatty Acids**

There also exist other non-essential members of the omega-3 and omega-6 fatty acid families, which the body can manufacture from the aforementioned essential fatty acids or which may also be derived directly from diet. The non-essential omega-3 fatty acids include docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) which are synthesized from ALA. Cold-water fish oils contain large amounts of these fatty acids. The non-essential omega-6 fatty acids include arachidonic acid (AA) and gamma-linolenic acid (GLA) which are synthesized from LA. However, in certain cases the conversion from essential to non-essential fatty acid is not adequate. ALA and LA are converted to their 20 and 22 carbon metabolites via a series of shared metabolic pathways (Cook, 1991). Because they compete for the same metabolic enzymes, the dietary omega-6:omega-3 ratio as well as the absolute amounts of these precursor fatty acids in the diet are important considerations (Wainwright, Jalali, Mutsaers, Bell & Cvitkovic, 1999). Inadequate conversion can also arise if availability of necessary cofactors in the reaction process – vitamins C, B6, B3, zinc, and magnesium – is compromised.

### **Neurophysiology of LCPUFAs**

The long chain polyunsaturated fatty acids, namely AA and DHA, are selectively incorporated and retained in the lipid bilayer of the brain and retina (Svennerholm, 1968). The quantity and diversity of LCPUFAs that are incorporated into membranes has an effect on the process of signal

transduction through effects on membrane fluidity and subsequently activation of membrane-bound proteins important in neuronal function and phototransduction (Fliesler & Anderson, 1983; Lauritzen, Hansen, Jorgensen & Michaelsen, 2001). DHA is a major constituent of synaptic end sites (Williats et al., 2000) while AA may influence neurotransmission through its function as a precursor of eicosanoids (Kurlack & Stephenson, 1999), modulators and mediators of a variety of biological processes (Seyberth & Kuhl, 1988). The importance of the availability of omega-6 fatty acids for normal growth and development has clearly been established (Innis, 1991), while the argument for the necessity of omega-3 fatty acids is based largely on functional outcomes, particularly with respect to its effects on the developing visual system (Connor, Neuringer & Reisbick, 1992). More specifically, there is substantial incorporation of DHA in the conversion of nerve growth cones to mature synapses, and delivery of DHA to the growth cones is therefore likely to be a prerequisite for the formation of mature synapses (Martin & Bazan, 1992). DHA is essential for normal brain development in animals and humans, such that inclusion of plentiful DHA in the diet improves learning ability (Horrocks & Yeo, 1999) while omega-3 deficiencies are reflected in impairments in learning and neurodevelopment (Moriguchi, Greiner & Salem, 2000).

### **Importance of LCPUFAs and Cognitive Development**

Infant cognitive development is affected by a complex interplay between genetic and environmental factors. Any scientific study examining the effects of breastfeeding on infant intelligence is confounded, for example, by the fact that type of infant feeding is highly correlated with social class and maternal education, which are also determinants of cognitive development (Drane & Logemann, 2000). Mothers who elect to breastfeed tend to be older, better educated, and from a two-parent family of upper socioeconomic class (Drane & Logemann, 2000). The very first trials were conducted to evaluate the effect of DHA supplementation only on preterm infants, who are more likely to benefit from supplementation than term infants (Auestad et al., 2003). Improved visual development was reported in several studies in infants that were randomized to a DHA-supplemented formula, while those that were randomized to unsupplemented formula failed to demonstrate optimal brain and retinal development (Carlson, Werkman, Rhodes & Tolley, 1993; Carlson, Werkman & Tolley, 1996; Uauy et al., 1994). However, some studies also found evidence of retarded physical growth in the DHA-supplemented groups (Carlson, Cooke, Werkman & Tolley, 1992; Carlson et al., 1996; Ryan et al., 1999).



Subsequent trials evaluated the effect of both DHA- and AA-supplementation on infant cognitive and visual development (Innis et al., 2002; O'Connor et al., 2001; Vanderhoof, Gross & Hegyi, 2000; Vanderhoof et al., 1999). The results were positive with no adverse effects on growth.

Since that time, there has been a continuing accumulation of evidence in both term and preterm infants to suggest that breastfeeding may have small but detectable improvements on cognitive ability during infancy. Makrides, Neumann, Simmer and Gibson (2000) found that Bayley's MDI and PDI scores were similar in infants receiving a placebo (no LCPUFA), DHA-supplemented, or DHA- and AA- supplemented formulations when assessed at 1 and 2 years of age. Breast-fed infants exhibited higher MDI scores than all formula-fed groups at 2 years of age. The Bayley Scales of Infant Development (BSID) is a standardized test used to gauge the development of small children. It has two components, the Psychomotor Development Index (PDI) and the Mental Development Index (MDI). The former assesses motor skills such as walking, jumping, and drawing; while the latter tests memory, the ability to solve simple problems, and language capabilities. The BSID is a common example of a variety of tests which may be employed to gauge cognitive development. Drane et al. (2000) compiled a meta-analysis of all studies that had been published over the last twenty years evaluating the association between type of infant feeding and effects on cognitive development. Of the studies that met with their evaluation criteria, a majority concluded that breast-fed infants exhibited increases in I.Q. on the order of two to five points when compared to their formula-fed counterparts. Most importantly, these advantages were maintained even after controlling for confounding factors. There is also evidence of dose-response relationships between the amount of breast milk supplied and developmental or cognitive gains (Lucas, Morley, Cole, Lister & Leeson-Payne, 1992). The greatest concern expressed was that many of the studies evaluated did not distinguish between exclusive and partial breastfeeding, which, given that breastfeeding was truly beneficial for infant intelligence, would bias conclusions towards the null effect (Drane et al., 2000). It should be noted that null effects tend to predominate in larger scale clinical trials of standardized test performance (Colombo et al., 2004). In a study by Paine, Makrides & Gibson (1999) designed to examine cognitive development in infants that were all initially breast-fed, no relation was found between the duration of exclusive breastfeeding and MDI scores at 1 year of age.

One important issue concerns the extent to which the benefits of breastfeeding on cognitive development persist beyond middle childhood. To date, most studies have examined these benefits in preschool children or

in children studied in the early school years. Less is known about the extent to which the benefits of breastfeeding on cognitive ability extend into adolescence and young adulthood. Horwood & Ferguson (1998) followed over 1000 children through their first 18 years of life to evaluate the effects of breast feeding on later cognitive and academic outcomes. Outcomes were assessed using a range of measurements including standardized tests, teacher ratings of performance, and academic outcomes in high school. Breastfed children had higher mean scores on tests of cognitive ability; performed better on standardized tests of reading, mathematics, and scholastic ability; were rated as performing better in reading and mathematics by their class teachers; and less often left school without educational qualifications.

### **Importance of LCPUFAs and Visual Development**

Visual development is commonly used as surrogate measure of brain development. DHA, in particular, is incorporated into the membrane of the photoreceptor (Anderson, Maude & Zimmerman, 1975). Visual development is often assessed by determining visual acuity, a measure of the smallest element that can be resolved, and may be assessed in infants by using gratings which consist of black and white stripes or checkerboard patterns. This can be measured by using behavioural or visual evoked potential (VEP) methods where a VEP is the electrical activity of the brain that is generated in response to a reversing contrast checkerboard or grating pattern. The VEP is recorded by an electrode placed over the occipital pole. Two recent studies came to contradictory conclusions regarding the effect of DHA and/or AA supplementation on visual development and function. In the first study by Makrides et al. (2000) no differences were found in visual acuity, as measured by VEP tests, among the formula-fed groups regardless of whether or not supplementation was present. The authors concluded that the addition of DHA and/or AA to infant formulae does not influence visual development in healthy term infants. A second study by Birch et al. (2005) compared the effect on visual function in infants consuming either unsupplemented or DHA- and AA-supplemented formulae. VEP acuity was once again used as a surrogate measure of development. It was found that visual acuity of DHA-supplemented infants was consistently better than that of their unsupplemented counterparts. Interestingly, it was also found that red blood cell concentrations of DHA were triple that of unsupplemented infants by 39 weeks. It has been suggested that in formula-fed infants, the brain may not have sufficient stores of LCPUFAs to support the optimal maturation of the visual cortex (Morale et al., 2005).

Uauy, Hoffman, Mena, Llanos and Birch (2003) combined the results of fourteen trials looking at the effect of LCPUFA-supplementation in infant formulae on visual development. Analysis was performed with DHA dose as the independent variable and visual acuity at 4 months of age as the dependent. It was found that there was significant correlation between dosage received and measures of visual development. The authors conclude that despite the disparate methodologies and results between trials these results could be explained by taking more accurate measures of the amount of DHA consumed.

### **Effects of LCPUFA Deficiency or Imbalance**

Until recently, commercially available infant formulae lacked preformed DHA and other omega-3 and omega-6 fatty acid metabolites. Much of the evidence for the importance of DHA in cognitive development as well as the effects of DHA deficiency has come from studies with animals (Catalan et al., 2002). García-Calatayud et al. (2005), have shown that DHA is positively correlated with rates of learning in rats, to the point that DHA supplementation is able to reverse the adverse effects of a diet low in DHA. Wainwright, Jalali, Mutsaers, Bell & Cvitkovic (1999) demonstrated that an imbalance in the dietary uptake of essential fatty acids retards behavioural development in mice. In order to assess outcomes that may be related to extreme imbalances in dietary fatty acid supply, pregnant and lactating mice were fed a diet with a very low omega-6:omega-3 ratio, in which the omega-6 and omega-3 fatty acids were provided solely as LA and DHA respectively. The development of the pups was compared with that of pups of similar age and body weight that had been undernourished by rearing in large litters. Pups weaned on an imbalanced diet exhibited the same rate of learning in the Morris water-maze as pups weaned in large litters. Nonetheless, there was some sparing of function in both these groups, as they were behaviourally advanced relative to younger animals of a similar body weight. These results demonstrate that behavioural retardation from an imbalance of LCPUFAs is comparable to that of malnourishment. Not surprisingly, it was also demonstrated that addition of AA to the diet increased AA in the brain, and at high levels, decreased DHA. Conversely, increasing levels of DHA in the diet increased DHA, but decreased AA.

DHA deficiencies in humans are associated with learning disturbances as well as attention deficit hyperactivity disorder (ADHD), adrenoleukodystrophy, cystic fibrosis, phenylketonuria, unipolar depression, and the onset of sporadic Alzheimer's disease (Horrocks et al., 1999). DHA deficiencies are not only documented in pathological conditions; rather,

decreases in DHA levels in the brain are also observed with normal aging and are associated with the cognitive decline of aging (Horrocks et al., 1999). Evidence for the link between DHA deficiencies in humans and behavioural outcomes is taken from studies on ADHD and depression. It has been shown that boys with ADHD have significantly lower levels of omega-3 and omega-6 fatty acids in their red blood cells than age-matched controls, as well as symptoms characteristic of fatty acid deficiency, including: frequent urination, thirst, dry hair and skin (Stevens et al., 1995). It has also been shown that rates of depression are lower in populations where dietary intake of DHA is high (Mischoulon & Fava, 2000). In individuals with major depression, decreases in red blood cell levels of omega-3 fatty acids are observed, most notably of DHA (Mischoulon et al., 2000). These data, along with studies on the effects of supplementation with DHA and other omega-3 fatty acids, support the hypothesis that DHA may have psychotropic effects. As such, DHA is under current consideration for its potential therapeutic value as an antidepressant and mood stabilizer.

### **Cholesterol**

Breast milk is rich in cholesterol, while formula is not. While much of the research on lipid composition of human breast milk has focused on LCPUFAs, there is increasing evidence that cholesterol is also an essential factor in infant brain development. Cholesterol is an essential component of the plasma membrane and of myelin, a fatty sheath that surrounds the axons of neurons in both the central and peripheral nervous systems allowing for efficient conduction of nerve impulses. Cholesterol is also a necessary constituent for the formation of new synapses or synaptogenesis (Mauch et al., 2001), a process that is integral to neurodevelopment, through its influence on neurite outgrowth (Dietschy & Turley, 2001) and the clustering of postsynaptic receptors (Teter et al., 1999; Yankner, 1996). Breast milk has different effects on cholesterol levels at different stages of life. Owen et al. (2002) found that breast-fed infants had higher serum cholesterol levels than their formula-fed counterparts (Owen, Whincup, Odoki, Gilg & Cook, 2002). While there is no relation between type of infant feeding and cholesterol levels in childhood and adolescence, adults who received breast milk during infancy had a lower level of total cholesterol as well as a 14% lower ratio of low-density to high-density lipoprotein (LDL:HDL) ratio. Since serum levels of total cholesterol and low-density lipoprotein cholesterol are known risk factors for the development of coronary heart disease (Law, Wald & Thompson, 1994; Sheperd et al., 1995), these results provide evidence for an association between breastfeeding and reduced cardiovascular disease in later life.

Given the importance of cholesterol and fatty acids in neurodevelopment, factors that regulate their uptake and/or metabolism may also influence the developmental process. Apolipoprotein E (ApoE) is a cholesterol and fatty acid transport protein that plays an important role in the neuronal metabolism of these lipids (Wright et al., 2003). It is hypothesized to be involved in the redistribution of lipids among these cells and in the regulation of cholesterol homeostasis (Herz & Beffert, 2000; Mahley, 1988). The ApoE4 isoform of the protein has been shown to be associated with higher serum cholesterol levels (Wright et al., 2003). It has also been demonstrated to be an important risk factor for neurodegeneration as well as late-onset Alzheimer's disease (Bothwell & Giniger, 2000; Herz et al., 2000). However, despite its association with a terminal illness the E4 variant is very common worldwide (Herz et al., 2000). A recent study by Wright et al. (2003) found that the presence of the ApoE4 isoform at birth was correlated with better performance on the Bayley's MDI at 24 months of age. Carriers of the E4 allele demonstrated an improvement in score on the order of 4.4 points over carriers of other ApoE variants. This study provides evidence of the importance of regulatory mechanisms in influencing cholesterol levels in the infant and thus influencing cognitive development. Presumably, the beneficial effects of the E4 variant in early life would select for this variant to a greater degree than the detrimental effects that are seen to manifest in post-reproductive years.

Defects in cholesterol metabolism are known to alter brain development. The Smith-Lemli-Opitz syndrome (SLOS) is attributed to a mutation in the 7-dehydrocholesterol reductase gene (Witsch-Baumgartner, Loffler & Utermann, 2001), which encodes for an enzyme acting in the final step of the cholesterol biosynthesis pathway (Tint, 1993). Individuals with SLOS exhibit a marked deficiency in cholesterol levels in both plasma and tissue resulting in a failure to thrive, profound mental retardation, and high infant mortality rate (Tint et al., 1994). Elias, Irons, Hurley, Tint and Salen (1997) presented one of the first attempts to treat infants with SLOS using pure cholesterol in combination with two bile acids given to enhance absorption. All infants enrolled in the trial demonstrated increased physical growth and developmental progress, regardless of the extent of cholesterol deficit as measured pre-treatment and of the age of treatment onset. Parents, teachers, and clinicians all reported a decrease in hyperactivity, irritability and self-injurious behaviours, as well as an increase in attention span. This study, taken in conjunction with the evidence provided above, is powerful evidence for the importance of cholesterol in infant cognitive development and raises the possibility that infants may benefit from cholesterol-supplementation of formulae. There have been no studies to date assessing the effects of cholesterol-supplementation.

### **Hormone and Growth Factor Content**

Breast milk contains a variety of growth factors and hormones at significant concentrations that have been hypothesized to be of developmental value (Polk, 1992). With respect to neurodevelopment of the infant such factors include neurotensin, nerve growth factor, sialylated oligosaccharides, and thyroid stimulating hormone (Banapurmath et al., 1996). Thyroid hormone is crucial for development of the brain during the fetal and neonatal periods, insufficient iodine for thyroid hormone formation leads to permanent developmental consequences (Laurberg, Nohr, Pedersen & Fuglsang, 2004). Hormonal iodine in breast milk occurs primarily as T4 (Dorea, 2002), while infant formulae are devoid of such maternally-derived factors but contain iodide (the inorganic form of iodine). The infant thyroid gland undergoes spontaneous development during the first three months of life (Bohles et al., 1993). In very preterm infants transiently low levels of T3 and T4 are commonly found in the blood, a condition referred to as hypothyroxinaemia (van Wassenaeer et al., 2002). Van Wassenaeer et al., 2002, examined whether or not breast milk could serve to ameliorate this deficiency. Despite the suggested importance of thyroid hormone on infant development, it was found that breast milk did not contain enough T4 to alter plasma concentrations in the breast-fed versus formula-fed infants. It has been suggested that iodide levels in breast milk may be lower than it was two decades ago, and that the recommended intake for mothers may need to be revised (Kirk et al., 2005).

### **Vitamin and Mineral Content**

In order to meet with FDA regulations, infant formulae must contain adequate levels of vitamins and minerals, including trace elements such as copper, iodine, manganese, and zinc. Vitamin K is added at higher concentrations than is found in breast milk to reduce the risk of neonatal hemorrhagic disease. In strict vegetarians, vitamin B12 is not present in breast milk in sufficient amounts to support normal brain development and supplementation, either of the mother's diet or with the appropriate infant formula, is required. These infants, if exclusively breast-fed, can develop a vitamin B12 deficiency within months of birth (Institute of Medicine, 1998). If left untreated, a deficiency in vitamin B12 can result in permanent and severe neurological damage with long-term effects on cognitive outcome (Graham, Arvela & Wise, 1992).

The main controversy with regards to mineral content in infant formulae is over the amount of iron which should be provided. Iron-fortified (12 mg/L)

as well as low-iron (2 mg/L) infant formulae are available on the market. In general, breast milk contains less calcium, iron (1 mg/L), and phosphate than infant formulae but provides these compounds with greater bioavailability such that they are taken up in adequate amounts to support normal development. Infants, however, cannot absorb all of the iron in formula milk and iron-fortified formulae are required to promote adequate iron uptake and maintain proper haemoglobin status (Stehlin, 1996). There is evidence to suggest that insufficient iron in the diet is the major determinant of iron deficiency (Pizarro et al., 1991), and that a significant decline of anemia among infants in the United States has been related to the shift from low-iron to iron-fortified infant formulae (Yip, Binkin, Fleshood & Trowbridge, 1987). On the other hand, symptoms such as abdominal discomfort, constipation, and diarrhea have also been attributed to iron intolerance of iron-fortified formulae. While low-iron formulae may alleviate these symptoms, they should be avoided as iron deficiency has severe consequences and may result in anorexia, delayed development of the immune system, failure to thrive, and impaired psychomotor and mental development (Moulden, 1994). Low-iron infant formulae have been recommended by the American Academy for Paediatrics for breast-fed infants less than six months of age in cases where supplementation is required. This recommendation is given on the hypothesis that the higher iron content of iron-fortified formulae could saturate the breast milk protein lactoferrin, which is involved in preventing the overgrowth of intestinal *Escherichia coli* (Lawrence, 1994). Support for this hypothesis comes from studies performed both *in vitro* and in guinea pigs (Baltimore, Vecchitto & Pearson, 1978; Bullen, Rogers & Leigh, 1972), however, a study by Scariati, Grummer-Strawn, Fein and Yip (1997) did not find an increased incidence of diarrhea in breast-fed infants supplemented with iron-fortified formula when compared with low-iron supplementation.

## **Contaminants in Breast Milk**

### **Environmental**

Most of the research on environmental contaminants in breast milk has focused on a group of chemicals referred to as persistent bioaccumulative toxic (PBT) chemicals. These include organochlorine compounds (i.e. DDT), dioxins (i.e. PCDD and PCDF) and furans, polybrominated diphenyl ethers (PBDEs), and polychlorinated biphenyls (PCBs). PBTs tend to be lipophilic and because breast milk is rich in lipids these compounds can be found at detectable levels in breast milk in populations around the world (Dekoning & Karmaus, 2000; LaKind, Wilkins, & Berlin, 2004).

Researchers often sample breast milk as a measure of community-wide contamination since it affords a sensitive and less invasive method of measurement than drawing blood or obtaining fat biopsies. Breast milk analysis is not used as a clinical tool (International Lactation Consultant Association, 2001). While there are standards for acceptable levels of pollutants (i.e., tolerable daily intake, TDI, values), research on the topic is not sufficient to allow the data to be used to predict health risks. PBTs are found in populations in industrially developed as well as in developing nations. The highest levels of contamination have been reported in women in agricultural areas that employ extensive use of pesticides (Hooper et al., 1999) and in women in remote areas, such as the Inuit populations, whose diet is heavily dependent upon marine species (Dewailly et al., 1993). Industrial and agricultural chemicals can be found in remote geographical areas where their use is extremely limited (LaKind et al., 2004). They are transported through the atmosphere and air currents to the Arctic regions (Wania & Mackay, 1993) where they then accumulate in humans and wildlife (Dewailly et al., 1993; Muir et al., 1995). The northern Canadian Aboriginal populations rely heavily upon fish and wildlife for subsistence and, as a consequence, exceed the recommended intake values for these compounds (Environment Canada, 2001). PCB levels in the breast milk of Inuit women have been found to be five times the levels found in southern Canada and among the highest in the world (Environment Canada, 2001). The Northern Contaminants Program organizes the efforts of the Canadian government to assess and decrease the use of these compounds.

*Polychlorinated Biphenyls (PCBs)*. PCBs have received widespread usage since the 1930s as dielectrics in capacitors and transformers, as well as a variety of other applications (World Health Organization, 1993). They have now either been banned or placed under severely restricted measures by the industrialized nations (Carpenter, 1998), but continue to persist in the environment due to their high biostability and resistance to chemical degradation. The main sources of continued exposure to PCBs are fish, fish products, and animal fats (Ribas-Fito, Sala, Kogevinas & Sunyer, 2001). Prenatally, these compounds are transferred via the placenta from the mother to fetus; postnatally, through breast milk. Infant formulae, by comparison, are free of these substances. It has been shown that environmental contaminants influence neurodevelopment. Organochlorine compounds like PCBs are neurotoxic, with studies in animals demonstrating that locomotory function (Bowman, Heironimus & Barsotti, 1981; Eriksson, 1996) as well as processes of learning and memory (Schantz, Seo, Moshtaghian, Peterson & Moore, 1981) can be adversely affected. Ribas-Fitó et al. (2001), conducted a review of seven studies



evaluating the effect of prenatal PCBs on development. During the first months of life, psychomotor development was found to be retarded while postnatal exposure through breast milk was not found to be related to adverse developmental outcomes. The authors concluded that while prenatal exposure has a subtle effect on neurodevelopment during infancy, the available data did not allow for an estimate of the degree of effect. PCBs also display estrogenic effects through their structural similarity to thyroid hormones (Longnecker, Gladen, Patterson & Rogan, 2000). They have been shown to alter thyroid hormone metabolism in animal studies, and similar effects have been demonstrated in neonates to background-levels of exposure (i.e. through mothers without occupational exposure to these compounds).

*Polybrominated Diphenyl Ethers (PBDEs).* PBDEs are another class of industrial contaminant. They are added to various foam and plastic products as a chemical flame retardant. PBDEs were the recipient of recent media attention when a Health Canada survey ranked Canadian women second only to the United States as containing the highest levels of these compounds as measured in breast milk (CBC News, 2004; Mittelstaedt, 2004). These levels were approximately five to ten times of those reported in other advanced industrial nations such as Japan and Germany. While breast milk levels of DDT, dioxins, and PCBs are on the decline (Craan & Haines, 1998), levels of PBDEs have risen with the increasing use of these compounds in consumer products (Noré & Meironyté, 2000; Ryan, Patry, Mills, & Beaudoin, 2002). PBDEs have been shown to affect the nervous system and thyroid hormone levels in animals studies, but there is little evidence of their effect in humans. A Health Canada assessment concluded that there is no immediate concern as the current levels in humans are below those which are shown to have an effect in animals and those flame retardants that are likely to pose the greatest health risk are already being phased out of use in Canada (Health Canada, 2004a; Health Canada 2004b).

*Lead and Mercury.* A number of heavy metals are detectable in breast milk, including lead and mercury (National Resources Defence Council, 2001). Exposure to toxic levels of these metals can result in neurotoxic and nephrotoxic impairments as well as in anemia (Gundacker et al., 2002). Unlike persistent bioaccumulative toxic (PBT) chemicals, metals are not lipophilic and therefore do not accumulate to higher concentrations in breast milk than in blood. Breast milk has been suggested to be a potentially significant source of lead exposure to the breast-fed infant (Silbergeld, 1991), but little research exists to quantify the extent of effect on infant health. Lead from past environmental exposure accumulates in the

bones and is released during pregnancy and lactation (Gulson et al., 1998). Because breast milk levels of lead are affected by both current and past exposure, lead levels are a problem in nations where lead usage is continuing as well as in nations where usage has declined (Abadin, Hibbs, & Pohl, 1997). Studies of lead in human milk have found concentrations ranging over three levels of magnitude from  $<1$  to  $>100$   $\mu\text{g/L}$  (Ettinger et al., 2004). Ettinger et al. (2004) studied the relationship between lead levels in breast milk and infant blood through one month of age. It was found that breast milk lead accounted for 12% of the variance of infant blood lead levels. The authors concluded that breastfeeding should continue to be encouraged because the absolute values of the effects were small within the studied range of lead concentrations. The only other large-scale study of breast milk and infant blood lead levels found that milk lead accounted for 10% of the variance blood lead at 6 months of age (Rabinowitz, Leviton, & Needleman, 1985). It is well established that there is an inverse relationship between calcium intake and uptake of lead. There is also evidence to indicate that intake of calcium supplements can reduce the amount of lead mobilized from the bones during pregnancy (Gulson et al., 1998b).

### **Pharmaceutical**

The list of chemical contaminants present in breast milk is not limited to compounds that are consumed unknowingly. Rather, it may include such substances as medications and their metabolites as well as common neurotoxicants like alcohol, caffeine, and nicotine (Golding, 1997). Neonates are particularly susceptible to the effects of these compounds because of immature hepatic and renal function, limiting the rates of degradation and excretion, and leading to accumulation of toxic levels over time (Buist, Norman & Dennerstein, 1990; Morselli, Franco-Morselli & Bossi, 1980).

*Anti-depressant Medications.* Enhanced vulnerability to psychiatric illness in the months after delivery raises the issue of whether or not (a) psychotropic medications will be administered to the breast-feeding mother, and (b) breast-feeding is to be continued if administered (Kendell, Chalmers & Platz, 1987). Lipid-soluble compounds pose a specific risk to the central nervous system since the neonatal blood-brain barrier is also immature (Nurnberg, 1981). In neonates, lipid-soluble compounds can be found in the cerebral spinal fluid at 10 to 30 times the concentration of that found in serum (Nurnberg, 1981). Limited fat storage sites are another factor in contributing to higher circulating concentrations of lipid soluble contaminants in neonates (Rivera-Calimlin, 1987). Burt et al. (2001)

conducted and compiled the results of a Medline search of all available literature dating to 1955 on the use of psychotropic drugs by breast-feeding mothers. The search included all antidepressant and anxiolytic drugs. While all psychotropic medications have been found to enter into breast milk, they each pass into infant circulation to varying degrees (Burt et al., 2001). The authors concluded that the available data were insufficient to establish a working relationship between serum concentration of a drug and infant behaviour or development. They suggest that the decision to administer be made on an individual basis, with careful monitoring of infant status throughout. They further suggest that future trials employ standardized tools of assessment, in order to ensure that the results are readily transferable to a clinical setting. The latest review on the usage of medications during breastfeeding by Berlin & Briggs (2005) states that for a vast majority of these compounds there is no risk to the infant.

The data on selective serotonin reuptake inhibitors (SSRIs) are of particular interest, since SSRIs are currently the most commonly prescribed class of antidepressants (Burt et al., 2001). Berle et al. (2004) present the results of one of the most recent studies examining usage of SSRIs during breastfeeding and infant exposure. The authors found that drug levels in the serum of breast-fed infants were undetectable or low. There was also no evidence of adverse drug-related events in these infants. This study lends further support to previous literature indicating that breastfeeding should generally not be discouraged in women using SSRI antidepressants.

*Alcohol.* It has not been established what effects the consumption of alcohol during lactation may have on infant health and development. Because alcohol is excreted only to a limited extent in breast milk (Lawton, 1984; Mennella & Beauchamp, 1991) the occasional exposure is often considered insignificant (American Academy of Pediatrics, 1994; Kesaniemi, 1974). Nevertheless, there are studies which show that the presence of alcohol in breast milk affects infant behaviour. Mennella and Beauchamp (1991) found that the odour of the milk changes with alcohol consumption and, as a result, the infants suckled more vigorously but took in less volume overall. If the mother consumed non-alcoholic beer, there was no change in suckling pattern. It has also been demonstrated that alcohol consumption affects the sleep-wake pattern such that infants spent less time in the active sleep portion of the cycle (Mennella & Gerrish, 1998). Studies have also assessed the effect of alcohol consumption on infant development. Little et al. (1989) examined the relationship between moderate maternal use of alcohol during breastfeeding and the mental and motor development of the infants. Development was measured on the Bayley Mental Development

Index (MDI). Infants of mothers who consumed less than one drink per day, compared to other breast- or formula-fed infants, did not display any difference in cognitive development scores. However, a slight difference was detected in gross motor development at one year of age. Little, Northstone, & Gooding (2002) aimed to reproduce the results of this early study using a different but comparable sample population and the Griffiths Developmental Scales. At 18 months of age, they were unable to detect a deficit in motor skills.

### Summary

The evidence to date supports the hypothesis that feeding with breast milk over infant formulae provides the infant with a measurable advantage on some, but not all, scales of cognitive development. This advantage has been observed to persist into adulthood. Breast milk also contains a number of known hormones and promoters of neurodevelopment which infant formulae lack; however, their effect on intellectual development has not been quantified at a behavioural level. It is incorrect to say that formula-fed infants are at a lifelong disadvantage to their breast-fed counterparts, since cognitive outcome is influenced by a myriad of environmental, genetic, and social factors. It should also be taken into account that breast milk can contain detectable levels of known environmental and pharmaceutical contaminants, which can be transferred to the developing infant through breastfeeding. The present evidence should be taken as further support for the importance of educating the public on the benefits of breastfeeding, along with other factors necessary to raising a healthy and intelligent child.

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