# “Why marine Omega 3 fatty acids are important for the human brain!”

**RSC, Burlington House, Monday 7th December 2015**

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**SCI Lipids Committee,**

**Chair of GOEDomega3 Science Committee and Manager of Scientific Communications at DSM Nutritional Products Ltd**

# Declaration of Interest

- Dr Winwood is an employee of DSM Nutritional Products, a manufacturer of marine Omega 3 Fatty  Acids.
- Dr Winwood is chair of the scientific committee of the global trade organisation GOEDomega3.
- Dr Winwood is a member of the SCI Lipids committee
- Note: "This presentation represents the scientific opinion of the presenter and does not necessarily represent the position of SCI or GOEDomega3."

# Importance of Breastfeeding

Human milk represents the nutritional gold standard for infant nutrition and we strongly support the WHO recommendation that infants should be exclusively breastfed for the first six months of life to achieve optimal growth, development and long-term health. Thereafter, older infants and young children should receive nutritionally adequate and safe complementary foods, while continuing to breastfeed for up to two years or more. We believe that breastfeeding is an unequalled way of providing ideal food for the healthy growth and development of infants and is also an integral part of the reproductive process with important implications for the health of mothers.

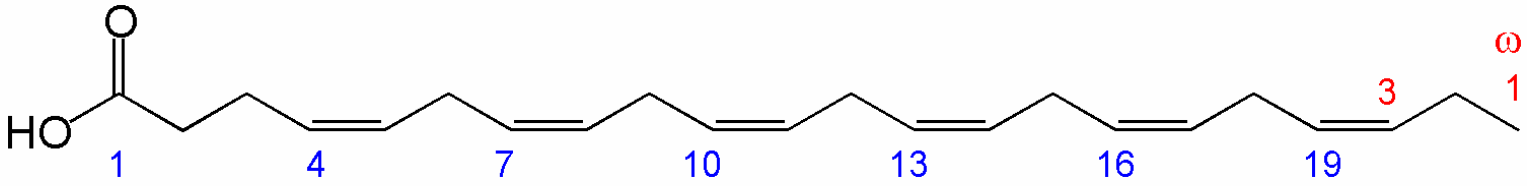
For many reasons, however, not every infant will be fed breast milk exclusively for 6 months. Indeed, some mothers choose not to breastfeed; some mothers may breastfeed only part of the time and a small percentage perhaps cannot breastfeed their babies. Infant formula, although it can never equal breast milk, is formulated in an attempt to ensure that the most nutritionally complete substitute possible is made available for babies who are not breastfed. Breast milk should be the nutritional gold standard by which formula milk should be assessed. The industry's goal over the years has been to continually improve the quality and safety of infant formula. We believe that components like DHA and ARA, as well as other infant nutrition innovations, help achieve this goal.

# Programme

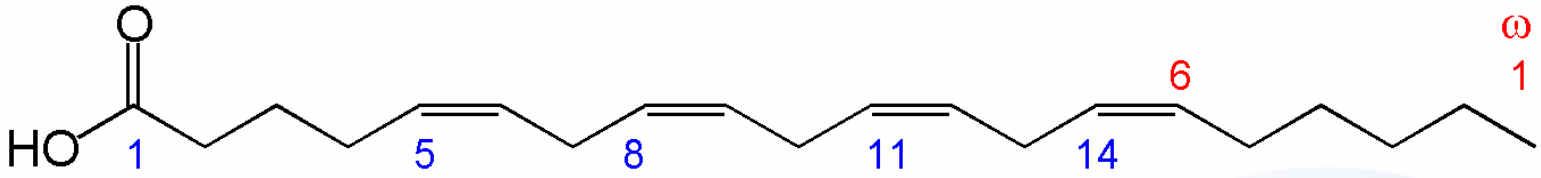
- Introduction
- How DHA and EPA work in the brain
- DHA and the Developing Brain
- The impact of DHA supplementation on age-related cognitive decline

# Omega-3's and Omega-6's

- Omega-3's are a broad group of fatty acids in which the first double bond exists at the third carbon




- Omega-6's are a broad group of fatty acids in which the first double bond exists at the sixth carbon



# YOUR BODY NEEDS OMEGA-3

- a very good fat, polyunsaturated and essential
- critical to overall health and well-being at all stages of life
- includes EPA + DHA, scientifically proven for brain, heart, and overall health
- primarily from fish and algae consumption

DSM
BRIGHT SCIENCE. BRIGHTER LIVING.

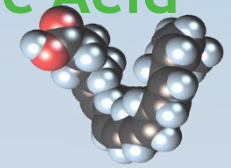
# YOUR BODY NEEDS OMEGA-3

**ALA Alpha-linolenic**

*Primarily from flax (linseed) / canola (rapeseed)*

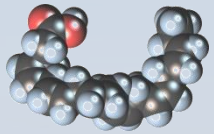
**EPA Eicosapentaenoic Acid**

*Primarily from fish*



**DHA Docosahexaenoic Acid**

*Primarily from fish / algae*



*majority of science for heart, brain health and normal growth & development*

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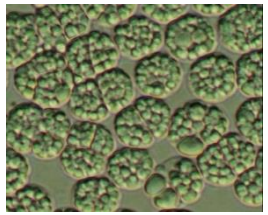
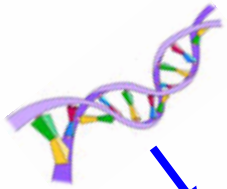
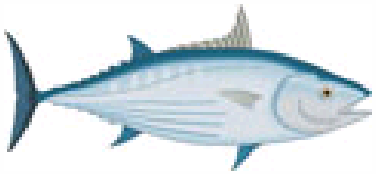
# Where do we get our Marine LC PUFA's?



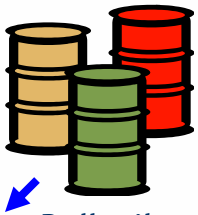
Marine microbes are primary source of PUFAs

LC PUFA genes

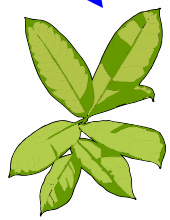




Fish accumulate LC PUFAs



Bulk oils



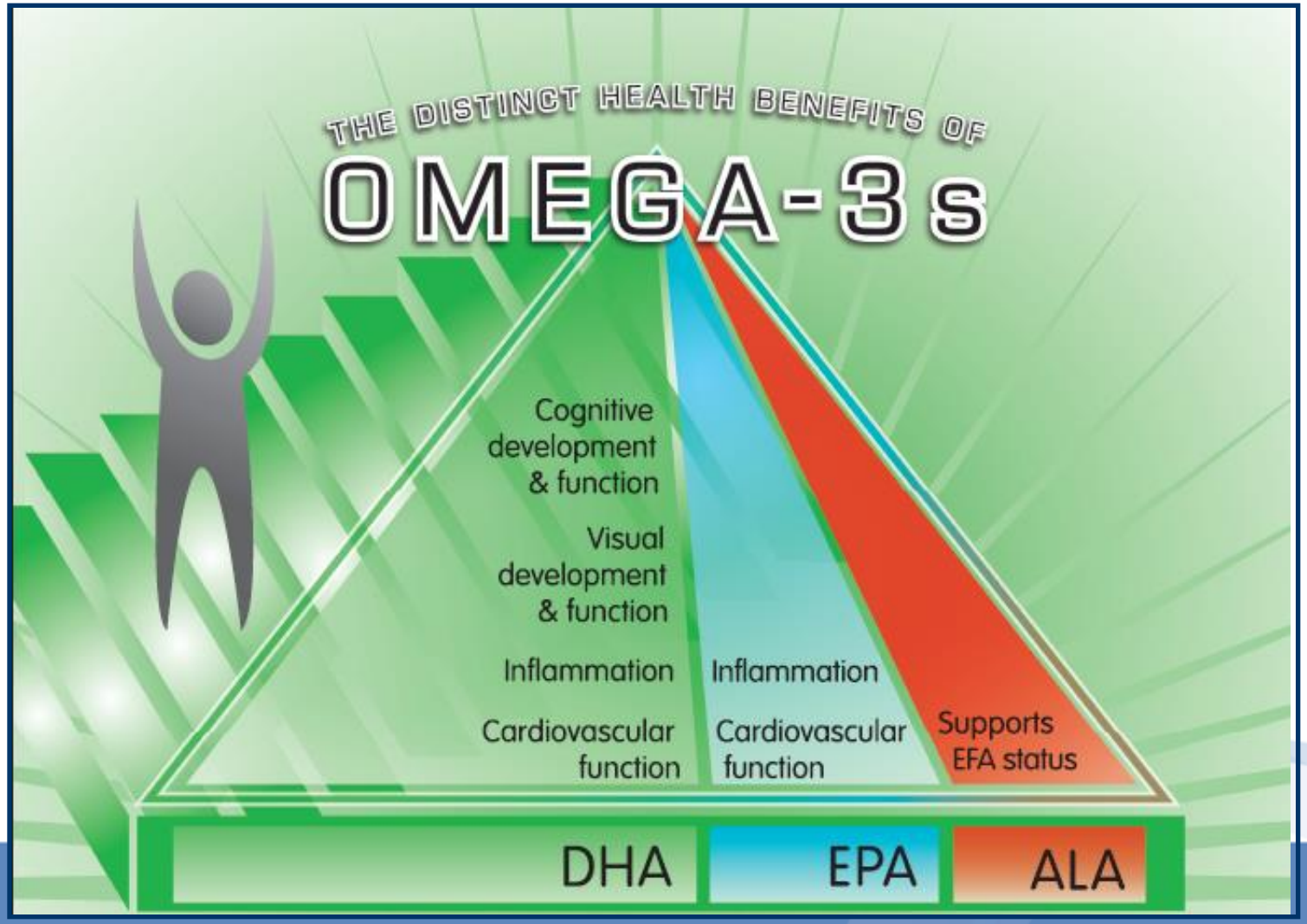
LC PUFA genes in plants, fungi, and animals

Supplements

Fish are main source of LC PUFAs in diet

Enriched food products

# Omega-3 Fatty Acids Are Not The Same



# ISSFAL Official Statement Number 5, 2009

"α–Linolenic Acid Supplementation and Conversion to n-3 Long Chain Polyunsaturated Fatty Acids in Humans'

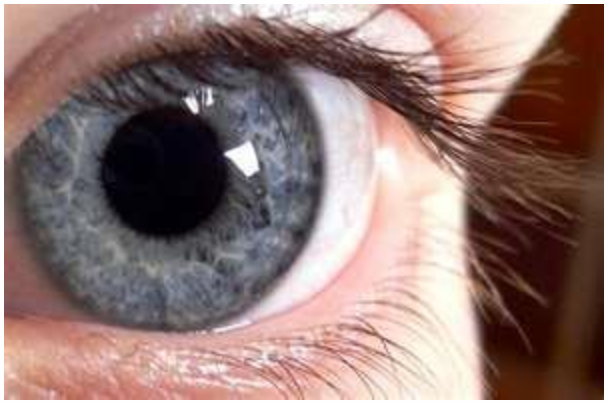
With no other changes in diet, **improvement of blood DHA status can be achieved with dietary supplements of preformed DHA, but not with supplementation of ALA, EPA, or other precursors.**

**(**International Society for the Study of Fatty Acids and Lipids, 2009)

# Marine Omega 3's

Are essential for:-

- GOOD CARDIOVASCULAR HEALTH
- DEVELOPMENT OF THE NERVOUS SYSTEM AND MAINTENANCE OF BRAIN HEALTH
- VISUAL DEVELOPMENT AND MAINTENANCE OF EYE HEALTH
- REDUCING INFLAMMATION



# LCP Dietary Sources

## Omega-6 FAs

Maize (corn) oil
Cottonseed oil
Safflower oil
Soybean oil

**LA (18:2)**
Linoleic acid

Poor levels of conversion in infants**

Eggs
Meat
Milk
Fungal Oil
from *Mortierella Alpina*

**ARA (20:4)**
Arachidonic Acid

## Omega-3 FAs

Linseed (flax) oil
Rape seed oil

**ALA (18:3)**
Alpha-linolenic acid

No known independent benefits on brain or eye development and function

Poor levels of conversion in humans*

Fish
Fish oil

**EPA (20:5)**
**Eicosapentaenoic Acid**

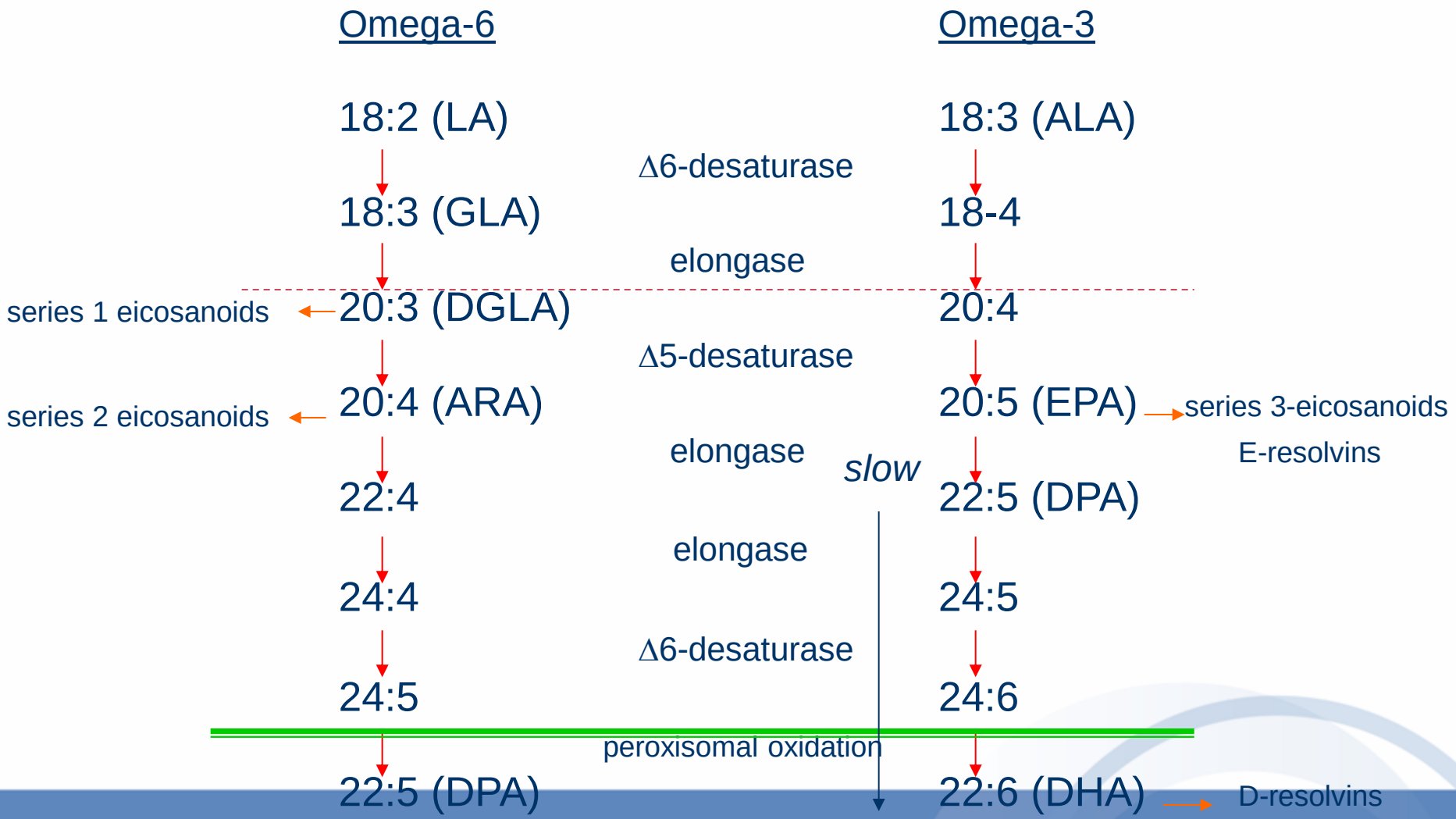
Negligible levels of conversion in humans*

Fish/Fish Oil
Fortified foods
Algal oil

**DHA (22:6)**
**Docosahexaenoic Acid**

* Brenna et al 2009, ISSFAL Position Statement No. 5
**Carnielli et al 2007; Pawlosky et al., 2006

# Long-chain Fatty Acid Biosynthesis




Lauritzen et al. (2001). *Prog Lipid Res 40,1-94.*

# IMPORTANT TO ‘RE-BALANCE’


**Hunter/ Gatherer**

**Agriculture**

**1900**
*initial industrialized food system*

**1970**
*completely industrialized food system = complete imbalance*

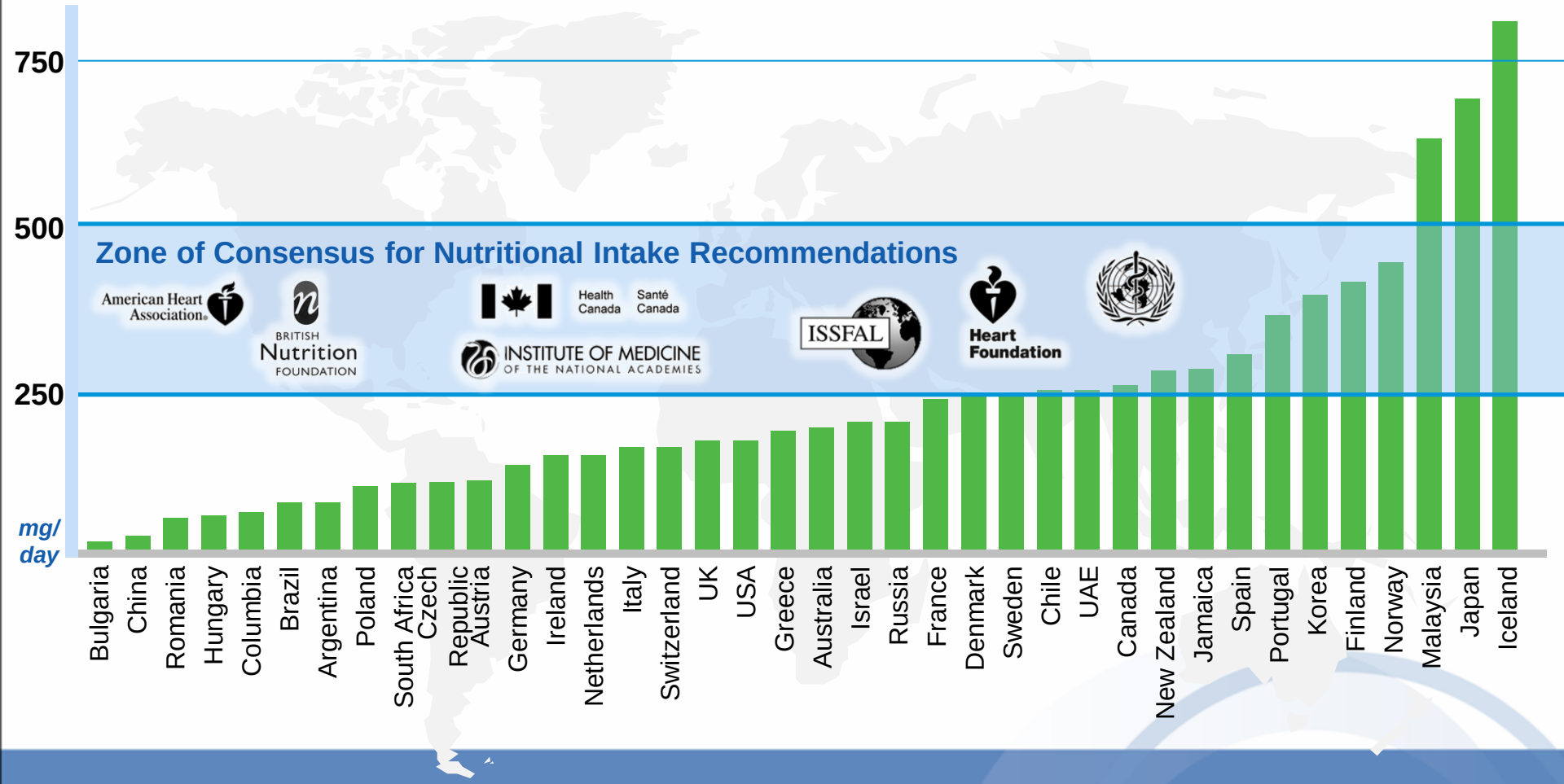
# The Omega 3 challenge

- In ancient times, when *homo sapiens* was a hunter  gatherer he had a plentiful supply of omega 3's through consumption of wild plants, seed and seafood.
- In the modern diet, we use lots of seed oils (soya, cottonseed, corn etc) which are dominated by omega 6 fatty acids.
- The seed oil producers prefer to have minimal omega 3's because they reduce the oils shelf life.

- **We need much more Omega 3's in our diet to maintain brain, eye and heart health**.
- The nutritional solutions are:
  - Eat more eggs
  - Eat more fish
  - Take EPA/DHA supplements

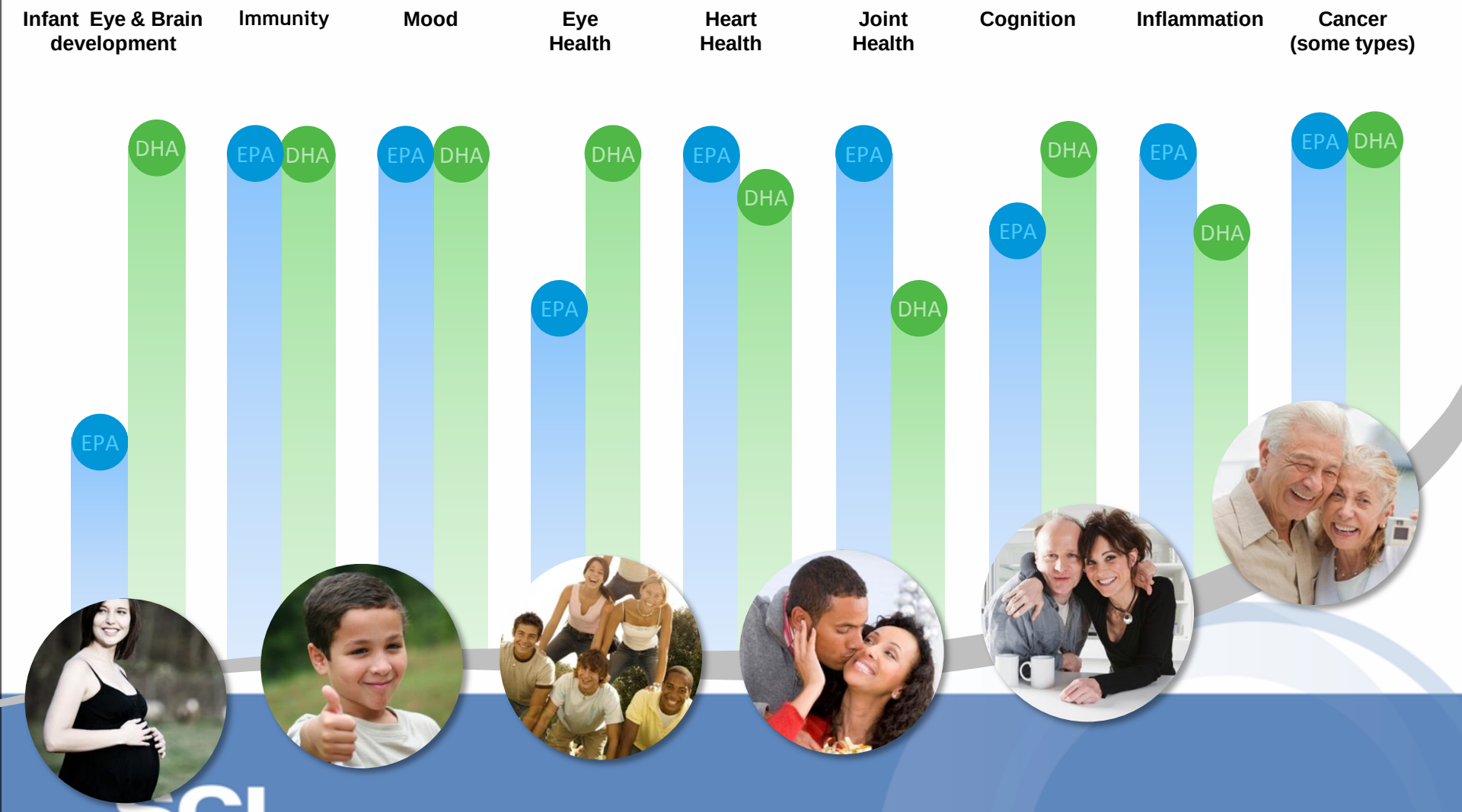

Source: Frik outdoors

# ESTIMATED AVERAGE DAILY INTAKES
## EPA and DHA



# OMEGA-3: A LIFETIME OF BENEFITS

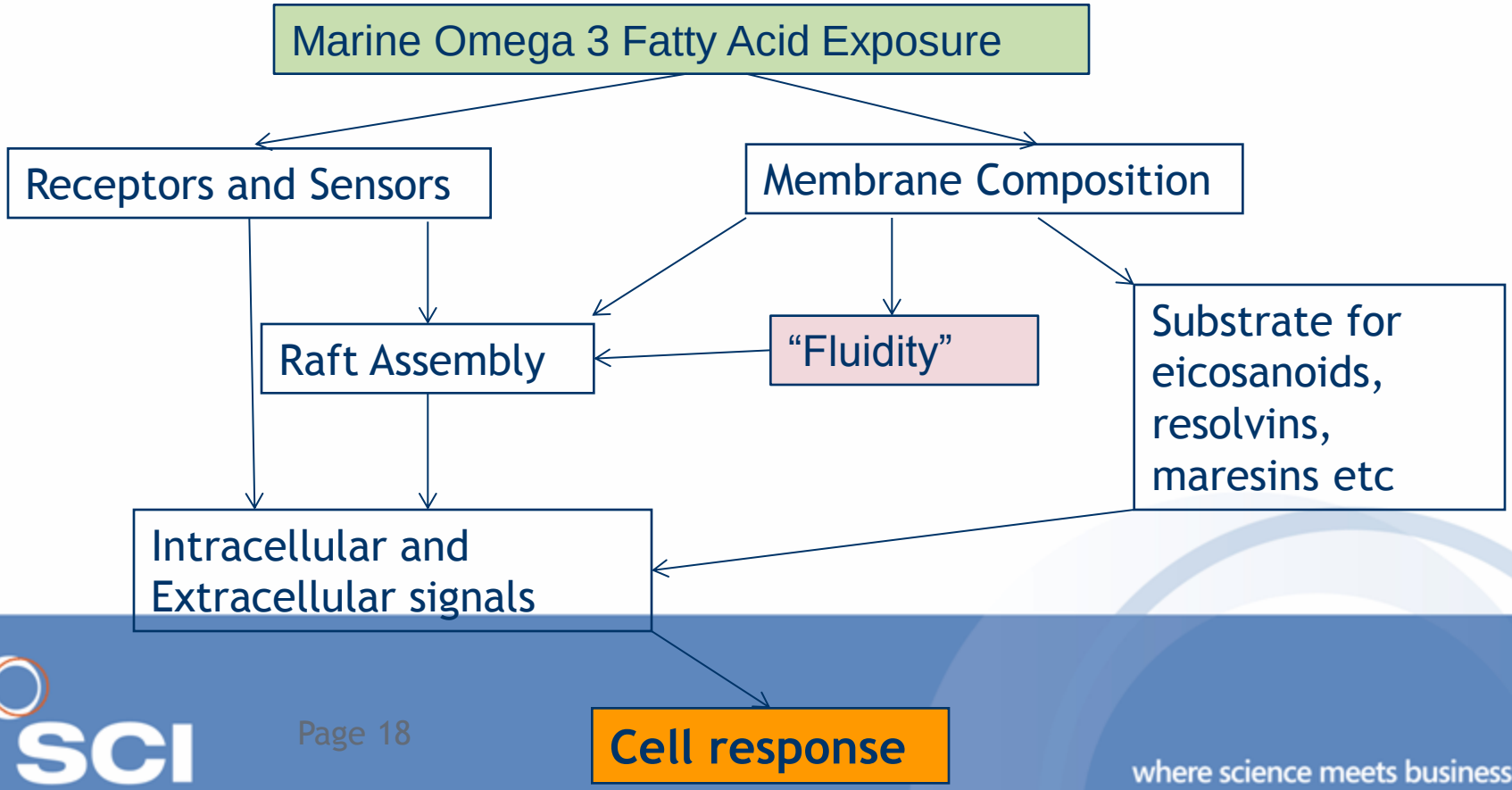
*Ongoing Research*



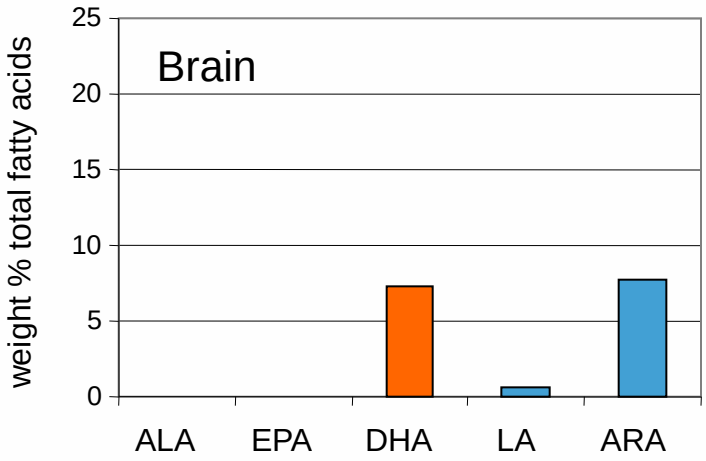

**Disclaimer: Not for purposes of claims

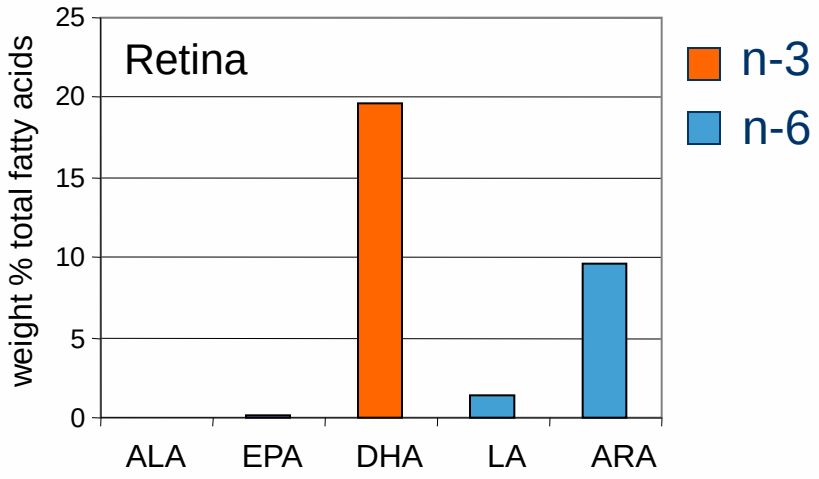
where science meets business

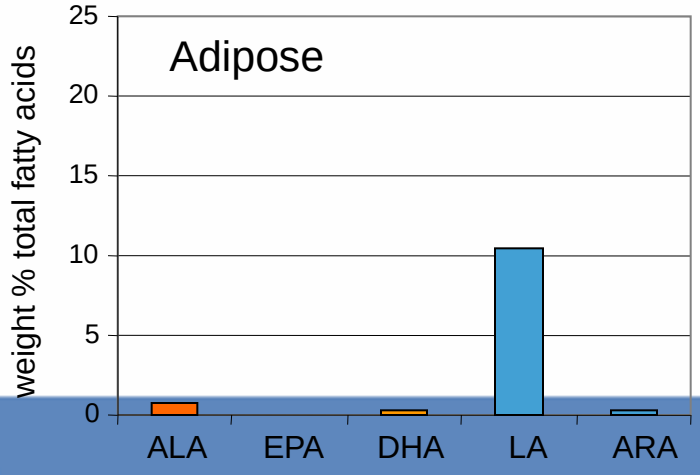
# Overview of mechanisms by which marine omega 3's can influence cell function (adapted from Calder. P., 2014 Eur J Lipid Technol 116(10) )

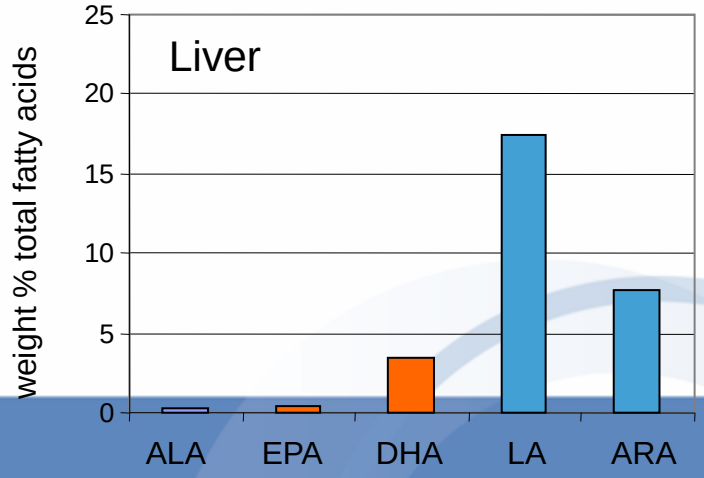


# LCPUFA content in various tissues




*Lauritzen et al (2001) Prog Lipid Res 40 (1-2):1-94*

# LC Omega 3's (DHA + EPA)

- Regulate blood flow
- Assist Immune Response
- Assist Hormonal Response

In addition **DHA** :=

- Is an essential structural component of the eye, brain and heart
- Facilitates and regulates electronic signaling
- Helps facilitate neurogenesis in the foetus

# The key differences between EPA & DHA

- DHA is required as a structural component in the cell membranes of essential organs in the human body i.e. the brain, nervous system, eye and heart.
- Some DHA is required for cell renewal at all stages of life BUT it is critical for infants, children and teenagers – and becomes important again in the elderly, when the body becomes less able to process dietary DHA and hence higher amounts are required to achieve homeostasis.
- The metabolites of EPA are essential in healing inflammation, promoting blood flow and fighting depression.  EPA Is not retained in the body so regular intake is ESSENTIAL.
- In infants only, it is important that the intake of DHA exceeds that of EPA or structural assimilation of DHA into tissues is impaired.

# Fish Oil History

- Fish oil has been in production since late18$^{th}$ century
- It was mainly used initially for soaps and ointments of various kind
- Whale oil, especially that of the **sperm whale** was high prized for use in oil lamps. It produced the best light with minimal spluttering.
- Until the 1960's the main use of fish liver oils was as a source of Vitamin A and D.
- Hydrogenated fish oils was widely used in the food industry to make "hard stock solid fats" until concerns over trans fat production largely eliminated production in Europe and North America in the last decade. It had been invented by Wilhelm Normann in 1901 in Herford, Germany.

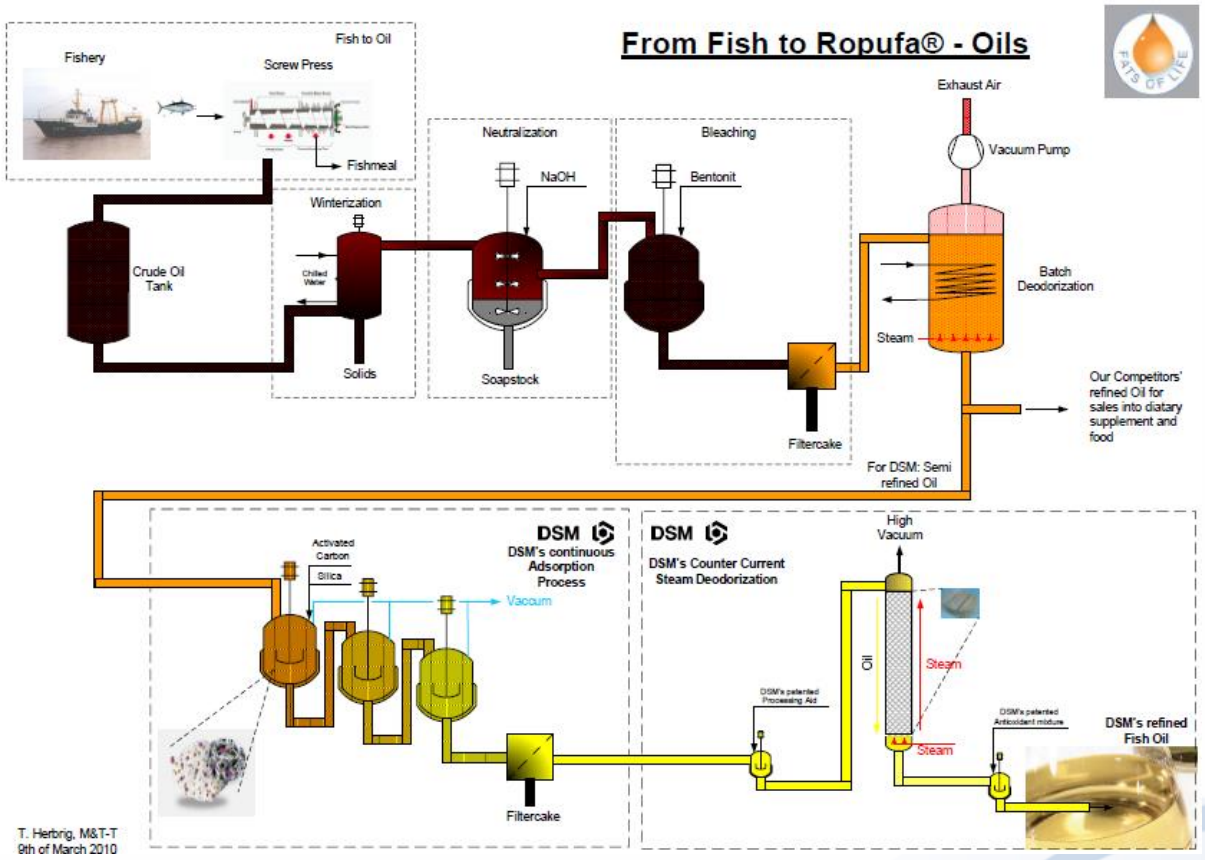
(source: Bryson W. 2010 in "At Home", Black Swan)

# Fish all over the world

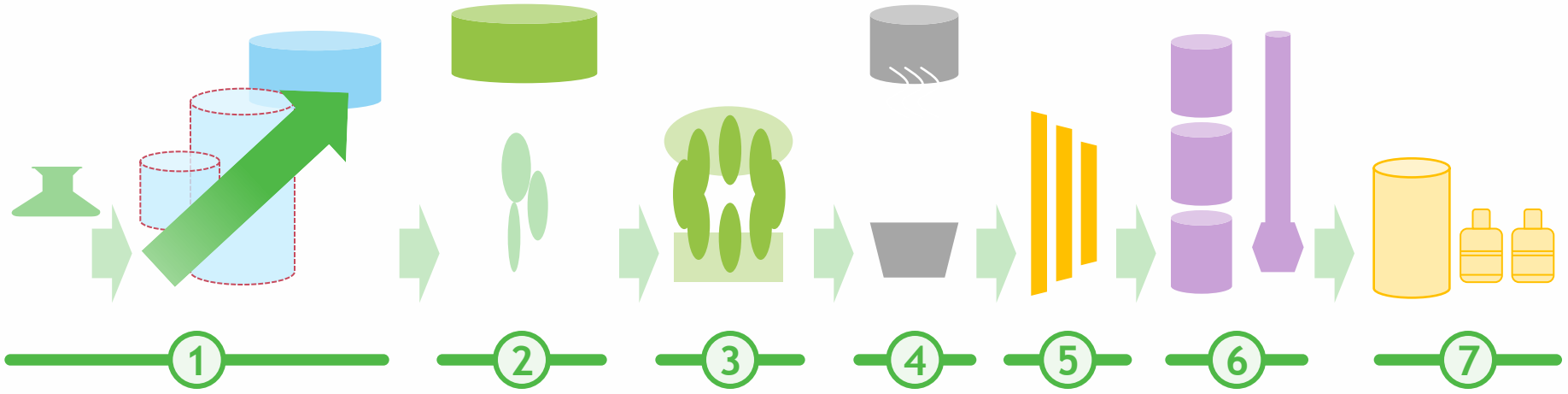

**There are just a few places where you can find fish rich in Omega-3**

where science meets business

# ROPUFA oils production process



# *life's*DHA™ & *life's*Omega™ Oil Production Process

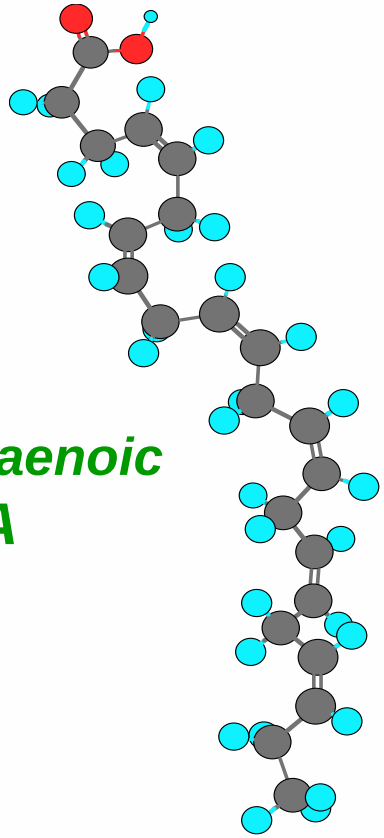


1. Seed Train
2. Main Fermentation
3. Centrifuge
4. Dryer
5. Extraction
6. RBD (refining, bleaching, deodorizing)
7. Blending & Packaging

DHA & *life's*Omega oil are manufactured through the fermentation of microalgae and is non-genetically modified. Product is Kosher and Halal
Controlled Manufacturing and very little variability in product costs

# How DHA and EPA work in the brain

# What is DHA?



***Docosahexaenoic Acid - DHA***

***22:6 ω3***

- Long chain omega-3 polyunsaturated fatty acid
- Important component of cell membranes
- ***Found in all tissues***; most abundant in neural, retinal and CV conducting tissue
- Facilitates synaptic transmission
- Supports myelination
- Ultimately influences the speed at which information is acquired and processed

# DHA: Recent Advances Cognitive Health

- **Muldoon et al 2010. In a sample of 280 middle aged adults (35-54 yrs)** Positive, linear association were observed for improvements of non-verbal reasoning, mental flexibility, working memory and vocabulary for DHA supplementation only. No effects were observed for ALA or EPA.. J Nutr 2010 doi: 10.3945/jn.109.119578

# EFSA Article 13 Health claims applicable to cognitive health

| | |
|---|---|
| Vitamin C | Contributes to normal psychological functions. (source of = 15% RDA min). |
| Vitamin B1 | Contributes to normal psychological functions. (source of = 15% RDA min). |
| Vitamin B2 | Contributes to the maintenance of the normal function of the nervous system. (source of = 15% RDA min). |
| Vitamin B6 | Contributes to normal psychological functions. (source of = 15% RDA min). |
| Vitamin B12 | Contributes to normal neurological and psychological functions. (source of = 15% RDA min). |
| Biotin | Contributes to normal psychological functions. (source of = 15% RDA min). |
| Folic Acid | Contributes to normal psychological functions. (source of = 15% RDA min). |
| Niacin | Contributes to normal psychological functions. (source of = 15% RDA min). |
| Pantothenic Acid | Contributes to normal mental performance. Contributes to normal synthesis and metabolism of steroid hormones, vitamin D and some neurotransmitters. (source of = 15% RDA min). |
| DHA | Contributes to the maintenance of normal brain function. (250 mg) |
| Iron | Contributes to normal cognitive function. (source of = 15% RDA min). |
| Zinc | Contributes to normal cognitive function. (source of = 15% RDA min). |
| Iodine | Contributes to normal cognitive and neurological functions (source of = 15% RDA min). |
| Magnesium | Contributes to normal psychological functions. (source of = 15% RDA min). |
| Potassium | Contributes to normal neurological function. (source = 15% RDA min). |
| Caffeine | Helps to increase alertness Helps to improve concentration (min 75mg per serving) |

# 2.6 BILLION YEARS AGO -> TODAY

BEGINNING > 2.6 B YRS BEFORE NOW -> 2000

ANAEROBIC SYSTEMS

OXYGEN

Trilobites

FISH

600 500 MILLION

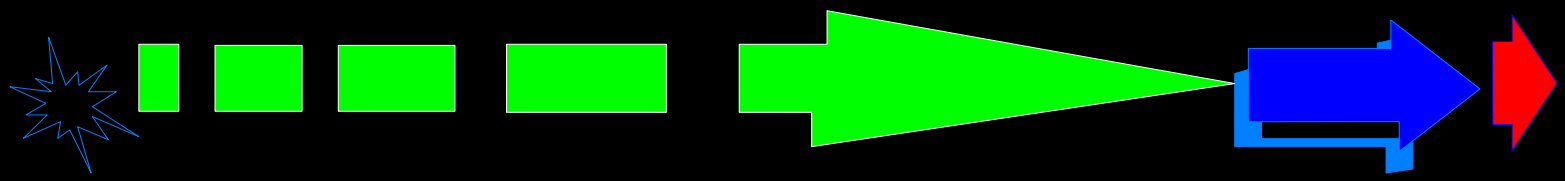
1.6 BILLION YEARS

TODAY

BLUE GREEN ALGAE

Amphibia

Reptiles



**MAINLY N-3**

Source: Prof. M. Crawford

# The sea is the only significant source of LC-PUFA's essential to our wellbeing

In evolutionary terms, we are the "aquatic apes" – it is the sea that made us clever!

.

Dolphins have the closest brain body weight ratio to humans,

They have a language and see in 3 dimensions with sonar.

# How do we think DHA works

- The omega 3 family are flexible. DHA has 6 double bonds which makes it the most flexible of all – able to adopt an **indeterminately high number of conformations**.
- DHA in the cell membrane lipids **keeps the cell wall flexible**, fluid and permeable.
- **Ions can more easily cross the membrane** and the specialised proteins in the membranes have to work harder to maintain the ionic gradients – which are key to driving the myriad of reactions within the cell. As a result, nerve impulses, signal reception and muscle contraction are sped up!
- The **molecular movement** of DHA will **speed up** many processes catalysed by membrane proteins (Hulbert, J. Exp. Biol. 2003, 206 p 2308)

# DHA allows electrons to move from one end of the molecule to the other (Prof Michael Crawford theory)

- The length and arrangement of double bonds in the DHA molecule means that UNIQUELY among the fatty acids, it will act as an electrical conductor. An electron can enter one end of the molecule and be transmitted along the molecule to the other end.
- This mechanism can help explain the how DHA assists in electrical signaling between neurones

# The DHA Molecule has a unique Pi cloud

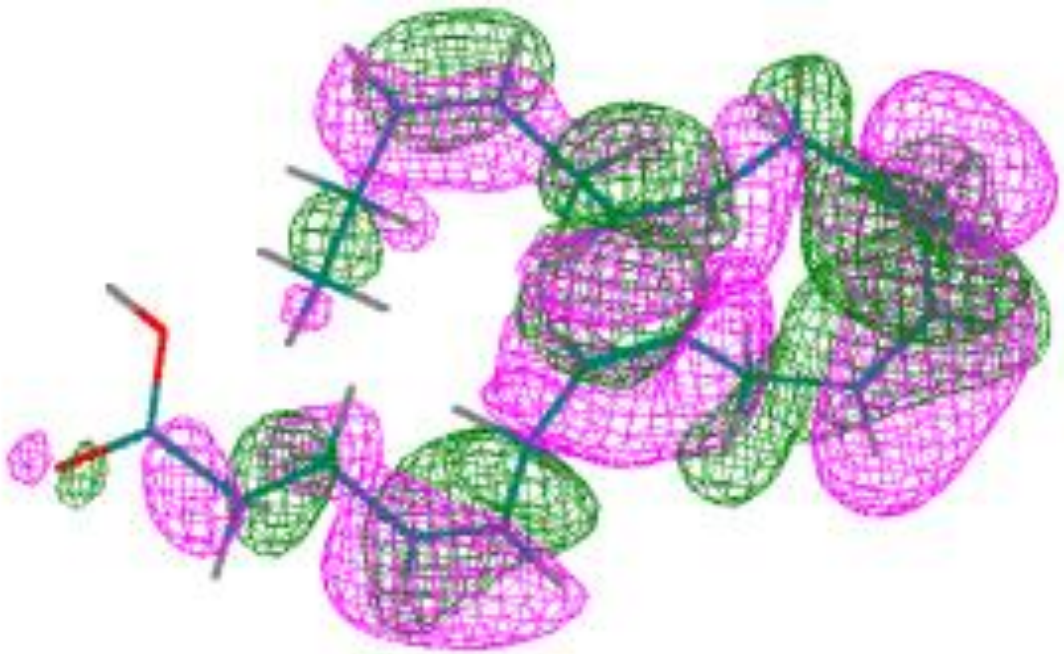


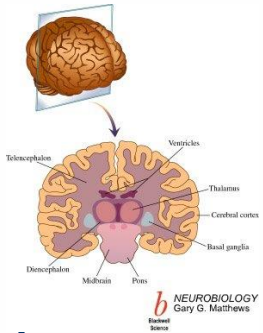
Fig. 6. Electron distribution around the DHA molecule high and low alternating densities. ($\pi$-bond energy different above and below planes; green lower, mauve higher energy).

**(source: Crawford et al 2008**, Fisheries for global welfare and Environment, 5th World Fisheries Congress pp57-76, published by Terrapub)

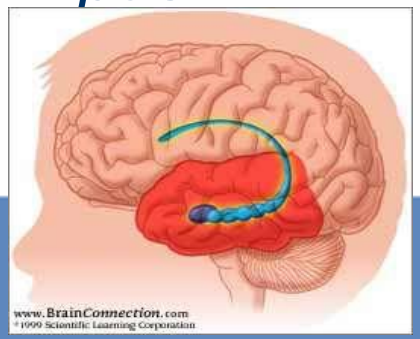
# DHA Distribution in the Brain

- DHA represents 10 to 15% of brain total fatty acids
  - **DHA** represents 97% of brain omega-3 fatty acids,
- DHA preferentially represented in cell membranes:

*frontal cortex*



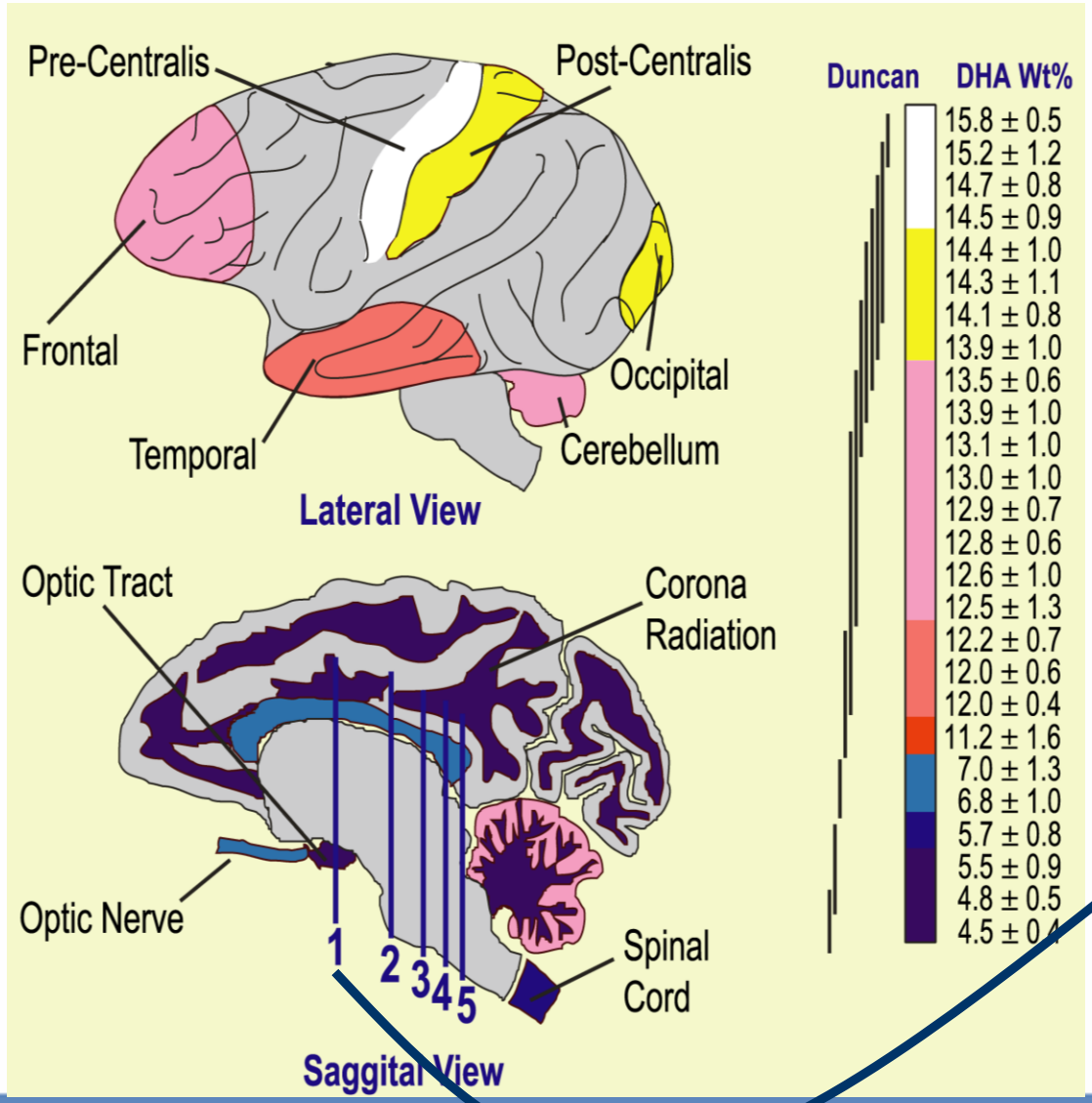

*hippocampus*

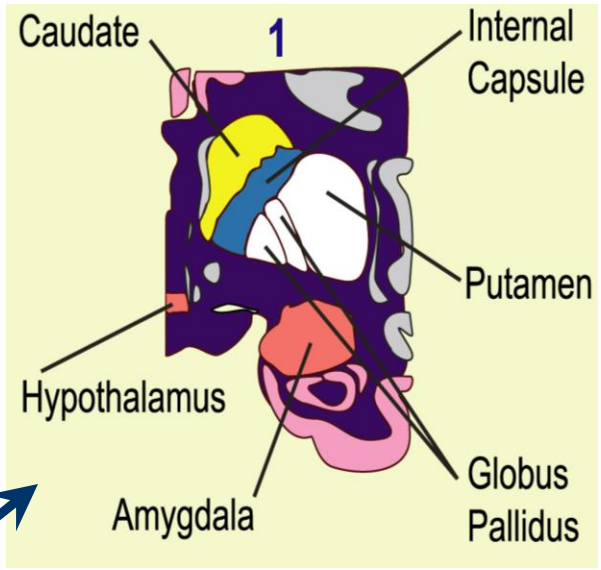



1. executive function
2. working memory
   - sustained attention,
   - problem solving
3. spatial learning
4. declarative memory formation

(ability to recall facts and events)

# *Where* is DHA in the Brain?




*Throughout.*

Diau, Nathanielsz, Brenna, et alia, BMC Medicine 2005.

# Role of DHA in Brain Structure and Function

## Structural Role

- Modulates function of signal transduction molecules, G-protein coupled receptors (e.g. rhodopsin)
- Integrated into brain phospholipids

## Functional Roles

- Converted to anti-inflammatory **docosanoids** (e.g. Neuroprotectins, Resolvins, Endocannabinoids & Anandamide)
- Participates in signaling via modulating G Protein Coupled Receptors (GPCR)
- Neuronal differentiation
- Myelination (Martinez 2000 Am J Clin Nutr. 71(1):376-385)
- Synaptogenesis
- Apoptosis (Kim et al., JBC)
- Modulates Ion Channels: Na+ transport (Kang & Leaf)

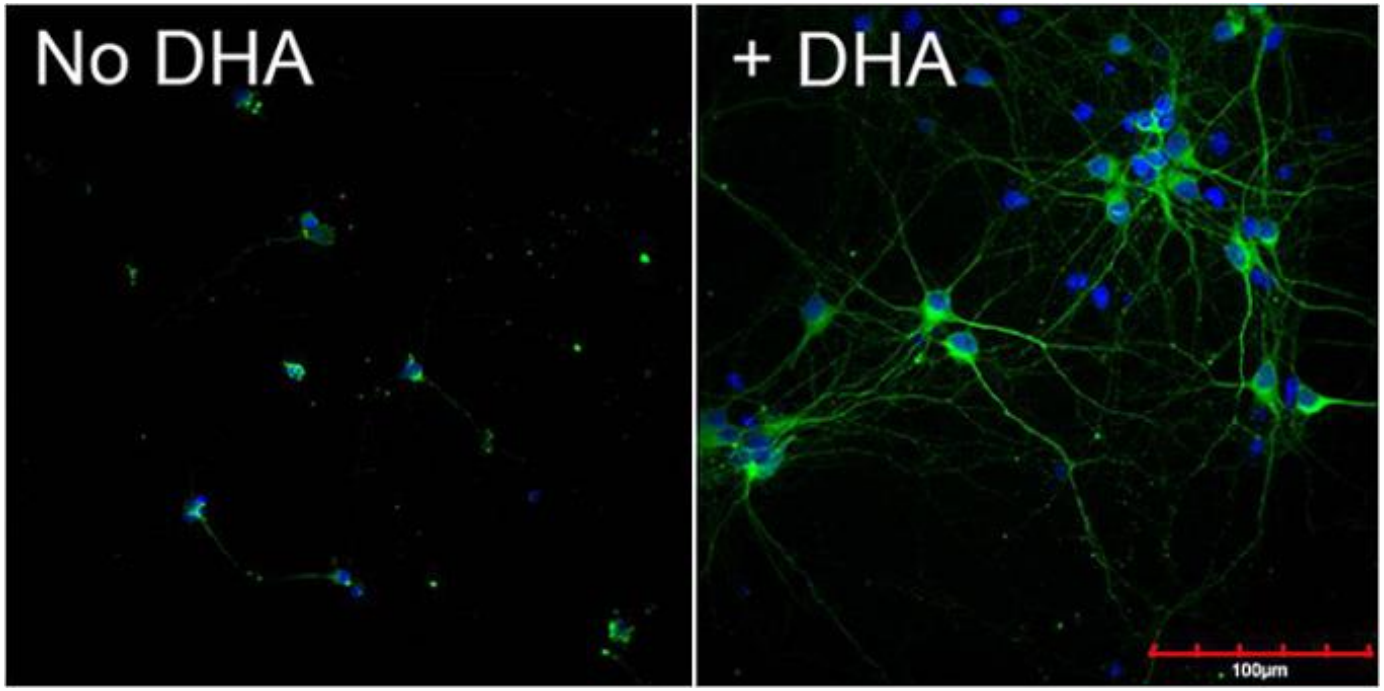
# How does DHA work in the brain

- Facilitates electrical transmission between neurones
- Source of essential brain messenger and anti-inflammatory molecules (e.g. resolvins, neuroprotectin D1)

Current theories:

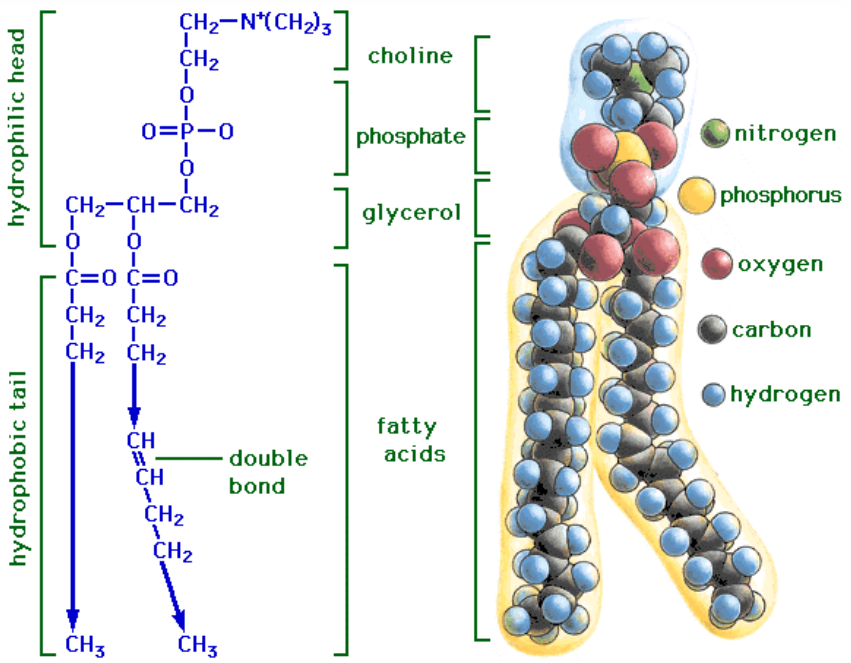
- The “almost infinite” possible conformations of DHA produces constant movement that is imparted to neural membranes
- The DHA molecule transmits electrons along its length and acts a semi-conductor (Crawford, 2008)
- Preserves telomere length of DNA (Farzaneh-Far,JAMA 2010)
- Reduces effects of free-radical damage in frontal cortex cells of the brain.

# DHA supports brain cell growth

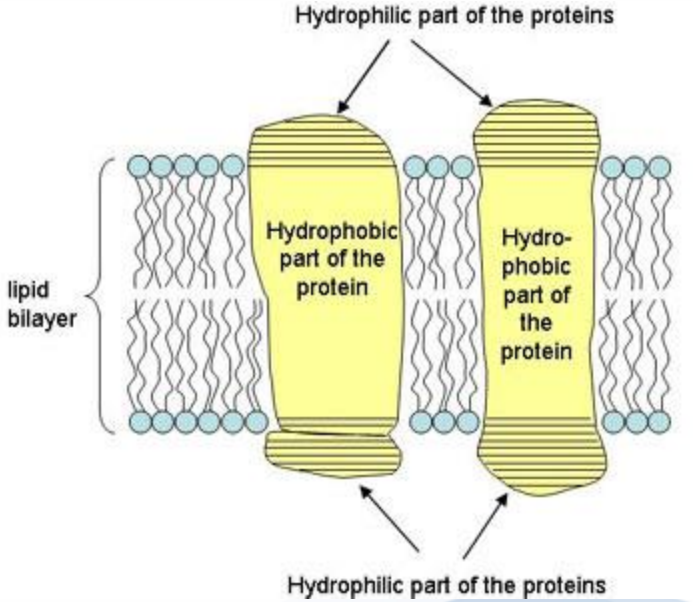



Cerebral cortex neurons exposed to DHA in cell culture extend branches and make connections much like they do during memory and developmental processes. (Unpublished Martek data, details available on request)

# Cell wall membrane bilayer

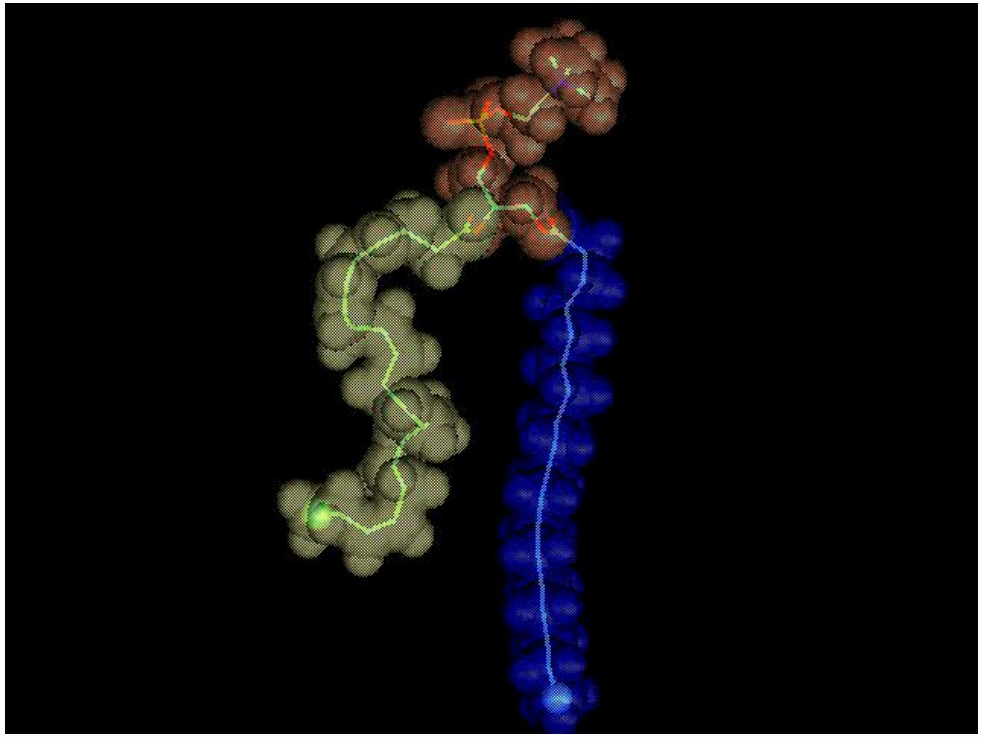



From www.agen.ufl.edu



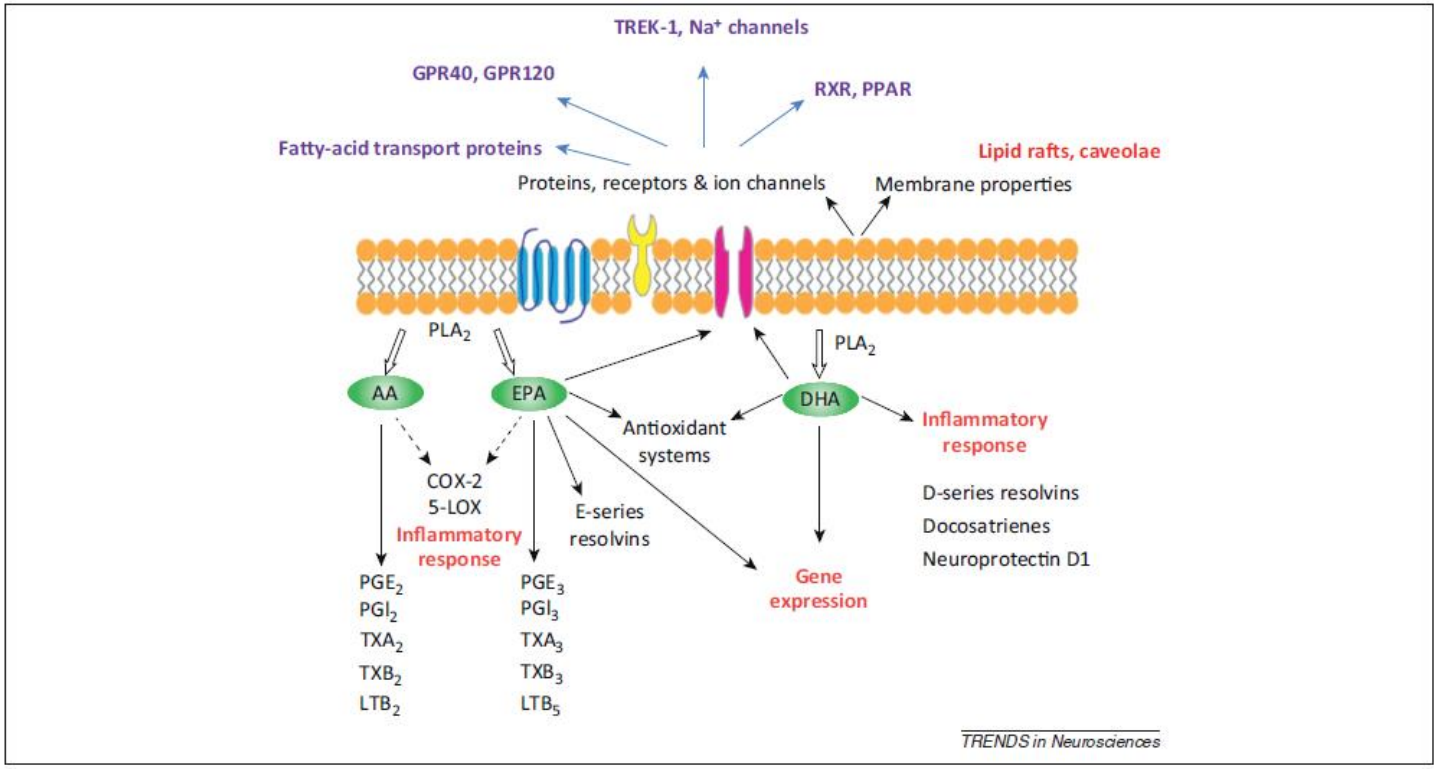

From www.aber.acc.uk/gwydd-cym/graffeg/biolgell/mosaig.eng.jpg

# DHA n-3 in a Lipid Bilayer- The Movie



Feller & Gawrisch, Curr. Opinion Struct. Biol. 15, 416, 2005

*Trends in Neurosciences* January 2014, Vol. 37, No. 1




# Omega-3 fatty acids and traumatic neurological injury: from neuroprotection to neuroplasticity?

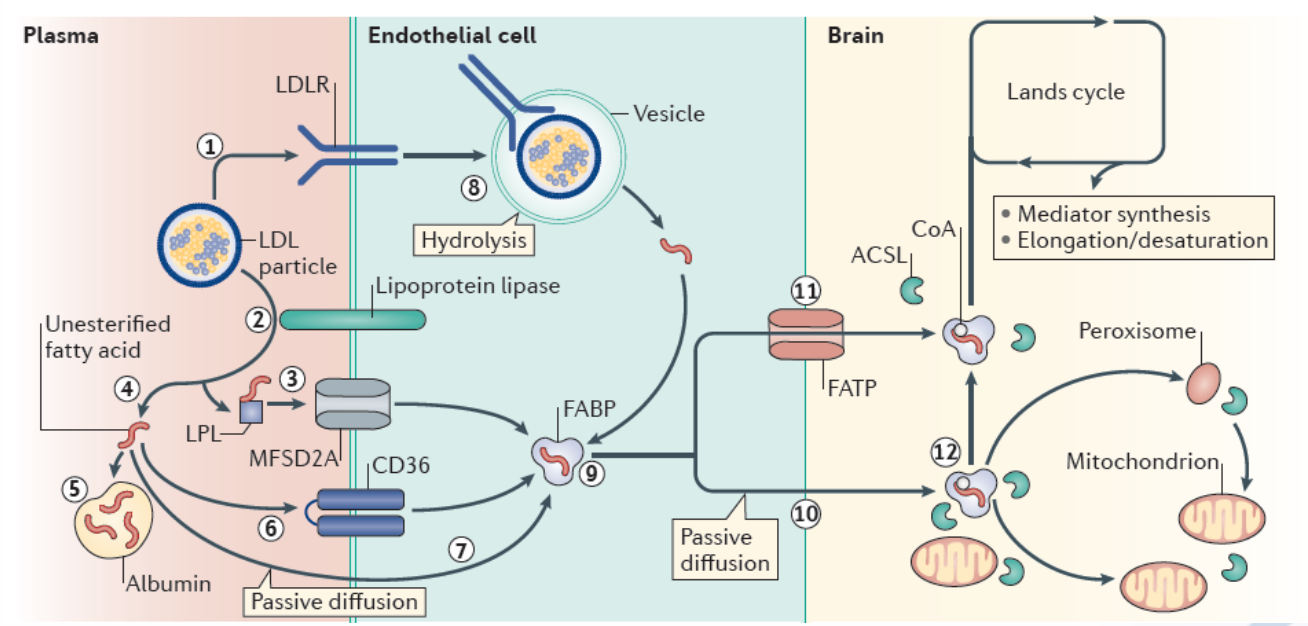
**Adina T. Michael-Titus and John V. Priestley**

Centre for Neuroscience and Trauma, Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London E1 2AT, UK

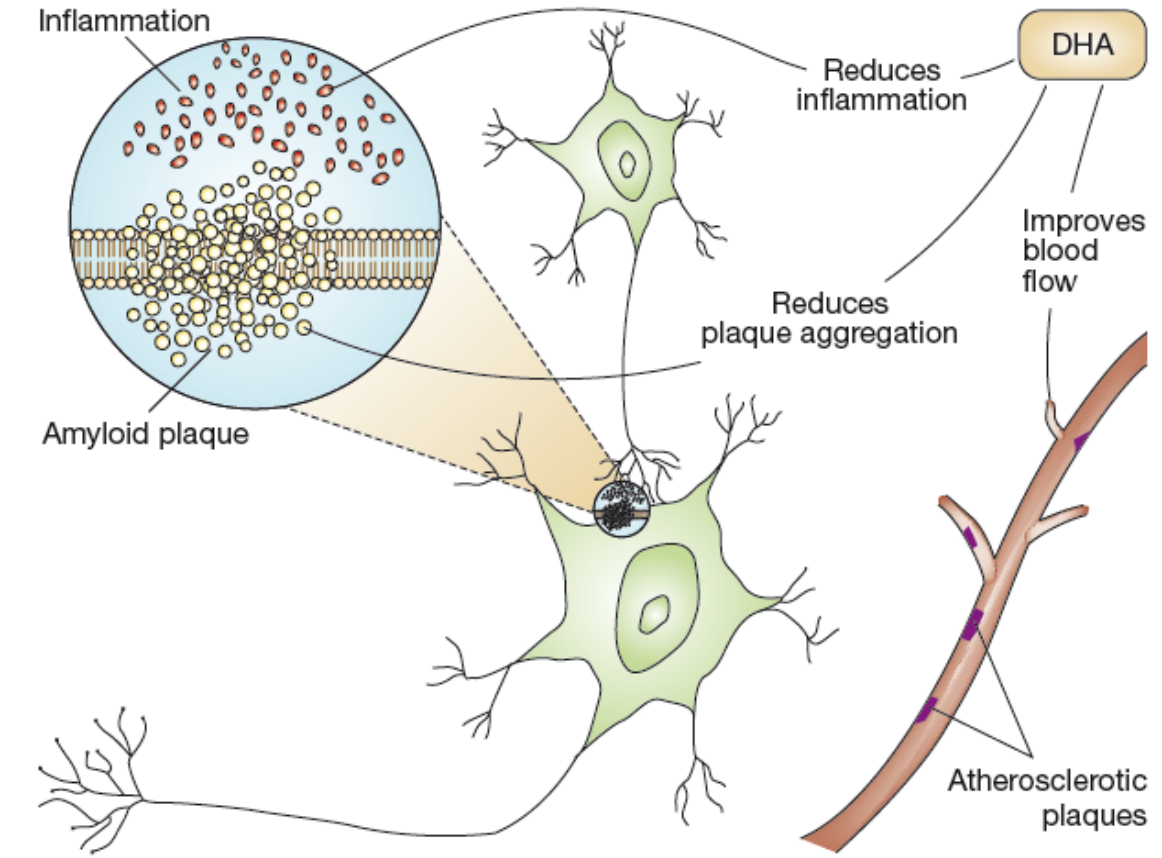
# Polyunsaturated fatty acids and their metabolites in brain function and disease

*Richard P. Bazinet[1] and Sophie Layé[2,3]*

Nature Reviews: Neuroscience December 2014 15:771-795

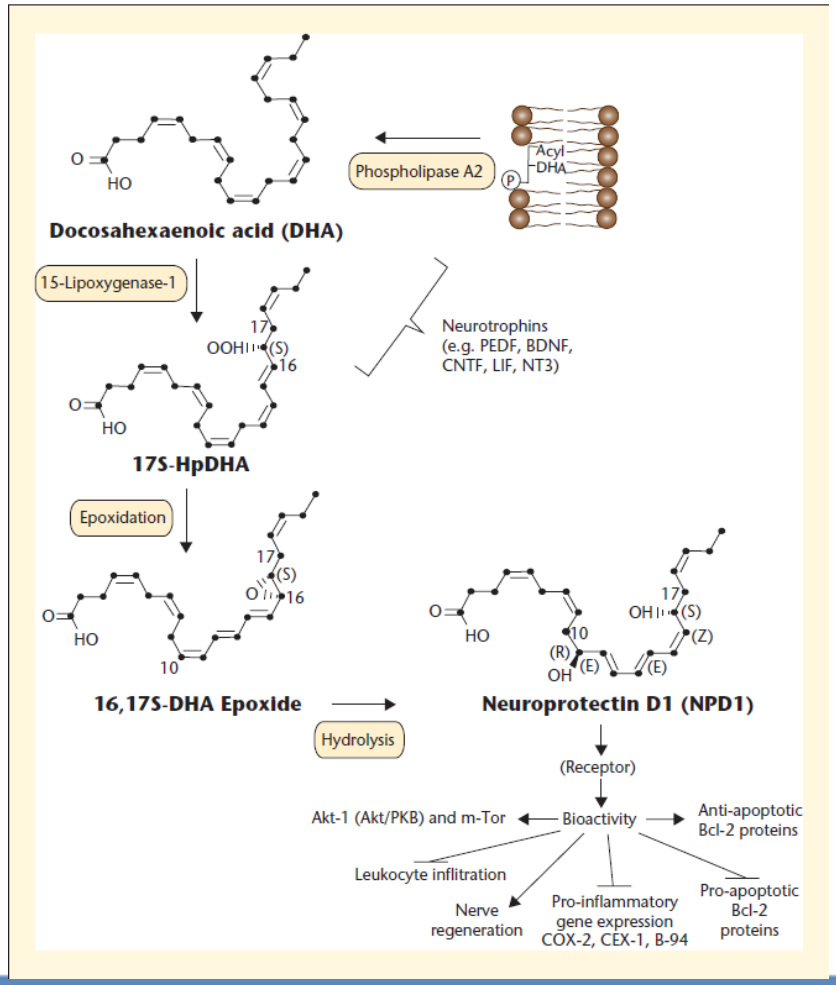


# Proposed Neuroprotective Properties of DHA




Source: Fotuhi et al, 2009, Nature Clinical Practice Neurology, 5(3):140-152

# Biosynthesis of Neuroprotectin D1 (NPD1)



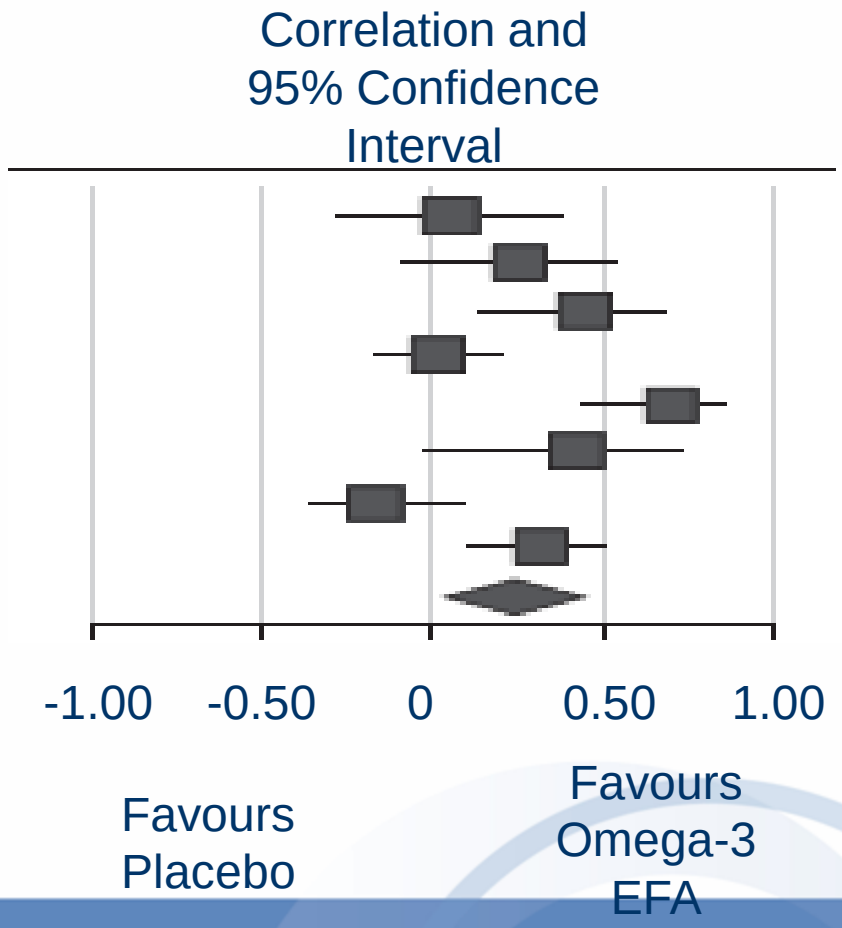

Source: Bazan M and Asatryan A, 2011, OCL18(4):208-213

# Meta-Analysis of Trials of Omega-3 Fatty Acids in Depression

Best-case analysis;

only 1-g/day doses were included

- **Freeman et al,** J, Clin Psych., 67:00, 2006



# Some key references for EPA and Depression

Sublette et al looked at 15 systematically selected trials in people with major depression disorder or suffering a major depressive episode in the context of bipolar disorder, they reported greater efficacy in individuals with major depressive disorder with supplements containing at least 60% EPA relative to DHA. They did not see beneficial results from DHA only. “Meta-analysis of the effects EPA in clinical trials in depression”. J Clin Psychiatry 2011;72:1577-1584

Low fish consumption, vegetable oil use was associated with increased risk of depression in Northern Finland. Tanskananen, Hibbeln et al Arch Gen Psychiatry 2001

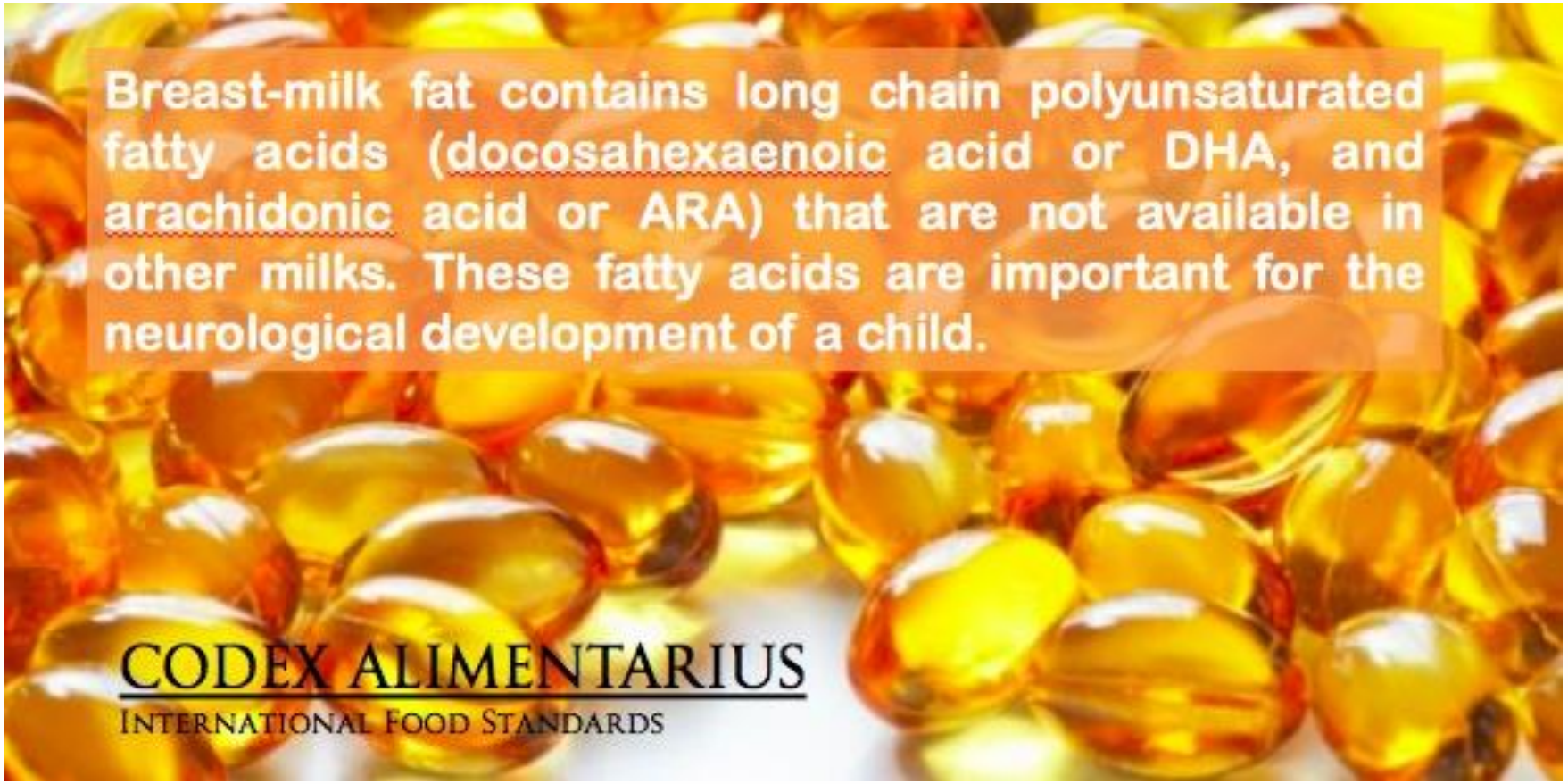
Beneficial effects of Omega-3 treatment of childhood depression were shown in a DB RCT with an age range= 8 to 12.5 years, treated for 16 weeks with a

monotherapy of 400 mg/d EPA + 200 mg/d DHA

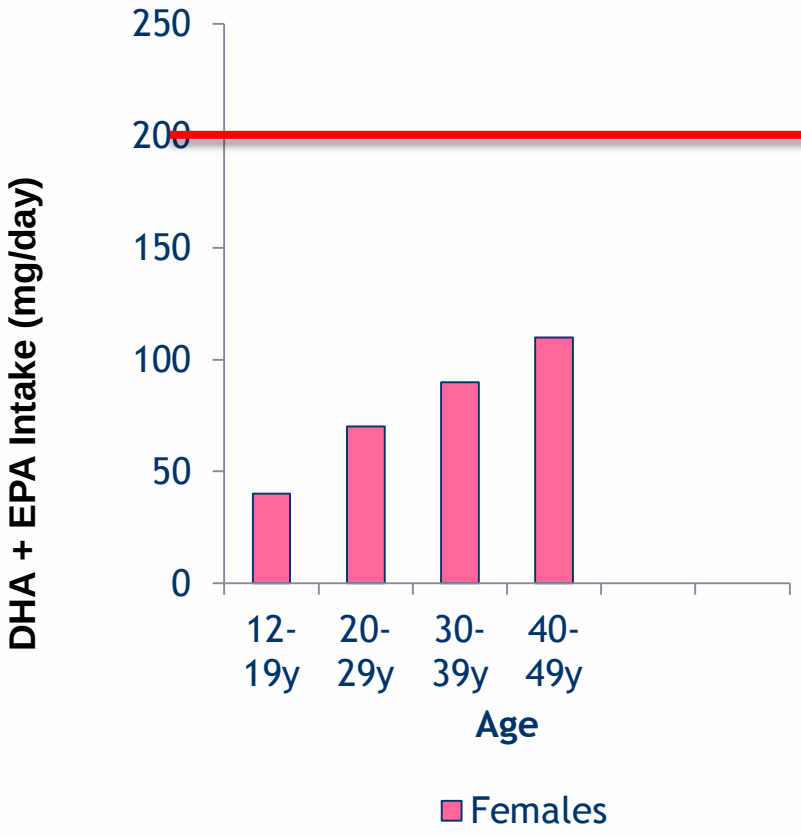
against placebo. Nemets et al Am J Psychiatry. 2006 Jun;163(6):1098-100

In the large Australian DOMINO cohort, The use of DHA-rich fish oil capsule supplementation during pregnancy did not result in lower levels of postpartum depression in mothers Makrides M., *JAMA. 2010;304(15):1675-1683*

# DHA and the Developing Brain


Breast-milk fat contains long chain polyunsaturated fatty acids (docosahexaenoic acid or DHA, and arachidonic acid or ARA) that are not available in other milks. These fatty acids are important for the neurological development of a child.
CODEX ALIMENTARIUS
INTERNATIONAL FOOD STANDARDS

# Dietary intakes of DHA during child bearing years fall below expert recommendations

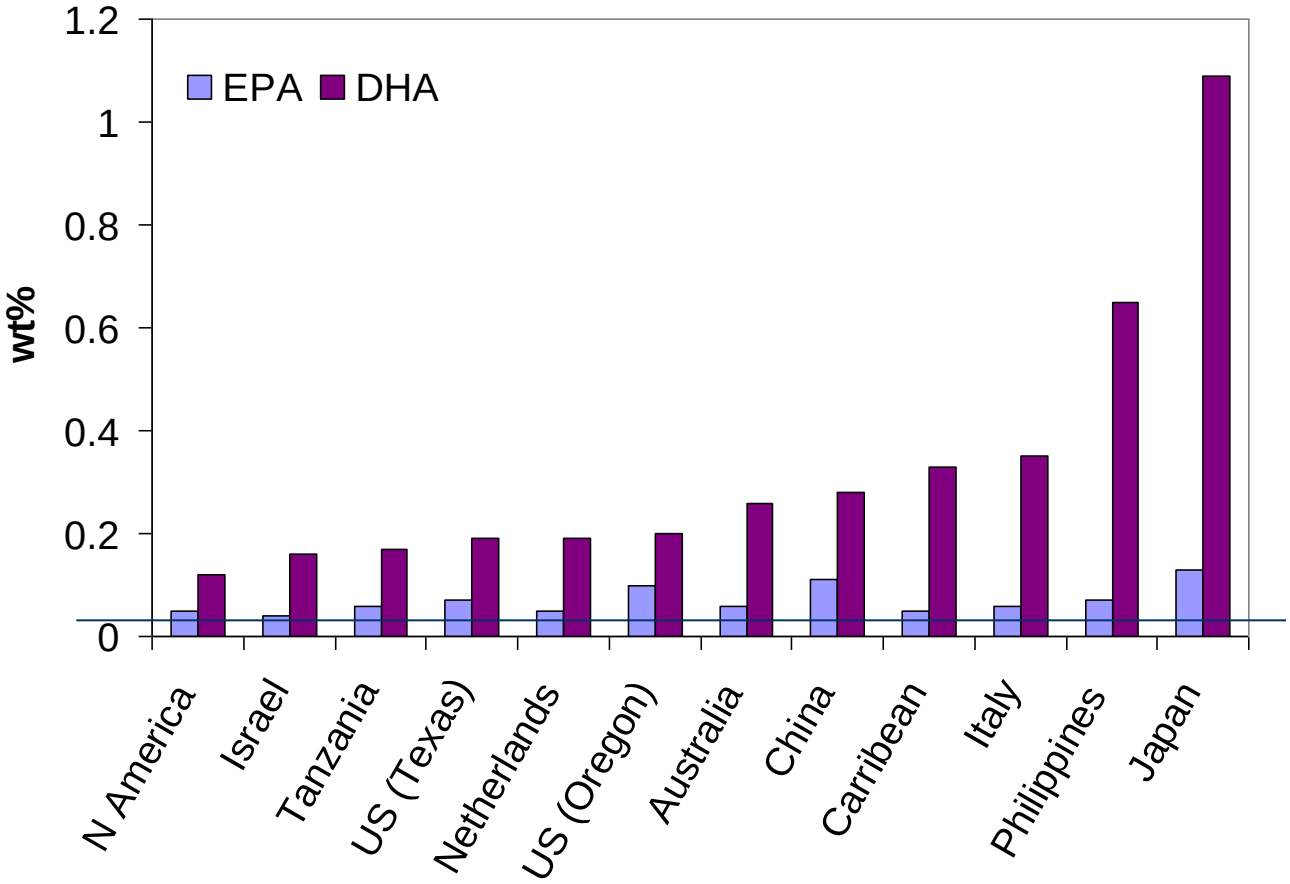



FAO/WHO, EFSA and others have set minimum intake standards for pregnancy and lactation

- **FAO/WHO – 200 mg DHA**
- **EFSA – 100-200 mg DHA incrementally over the standard recommendation for adult women**
- **March of Dimes – 200 mg DHA**

*What We Eat in America, NHANES 2009-2010*

# DHA and EPA Levels in Human Milk




*Yuhas, et al. Lipids 2006;41:851-858*

# Epidemiology studies of DHA in Childhood

## LCPUFA intake during pregnancy and lactation

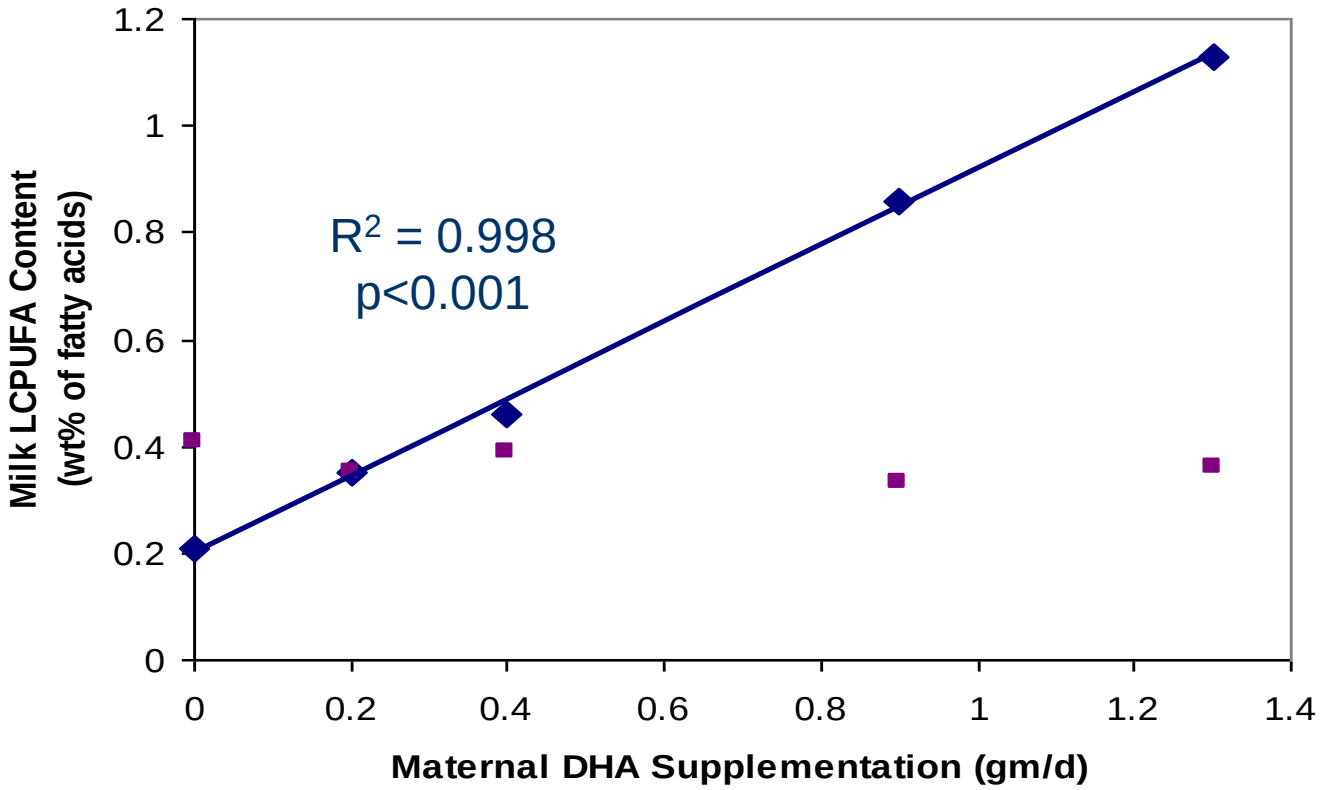
- **Hibbeln** et al (2007) (ALSPAC) – maternal seafood consumption <340 g/wk, ~3 servings) was associated with increased risk of low verbal IQ (lowest quartile) at 8 years of age

- **Oken** et al (2008) (Massachusetts cohort of 341 mother-child pairs (1999-2002)) – higher fish intake (>2 servings/wk) was associated with higher scores on the Peabody Picture Vocabulary Test and Wide Range Assessment of Visual Motor Abilities at 3 years of age

- **Budtz-Jorgenson** et al (2007) - – higher fish intake (>2 servings/wk) associated with cognitive performance at 7 and 14 years of age

- **Oken** et al (2008) (Danish National Birth Cohort wheren=25,446 children) – higher fish intake (58.6 g/day) and greater duration of breastfeeding (≥ 10 months associated with higher developmental scores at 18 months of age.

# Maternal Intake of DHA Determines Breast Milk DHA Content




Adapted from Makrides *et al* (1996) Europ J Clin Nutr

# DHA Impacts Visual & Cognitive Development between Birth and 2 Years

DHA

**Pregnant Women**

- Decreased look duration (12 months)
- Reduced distractibility (24 months)

*(Colombo et al. Child Dev, 2004. 75:1254-67)*

- Increased IQ

*(Cohen et al. Am J Prev Med, 2005, 29:366-74.)*

**Nursing Women**

- Sustained improvements in Mental and Psychomotor Development

*(Jensen et al. AJCN, 2005, 82:125-32.)*

**Infant Formula**

- Visual Evoked Potential/Visual Acuity

*(Uauy et al. J Pediatr, 2003, 143:S17-S25.)*

- Improved mental and psychomotor development

*(Birch et al. Dev Med Child Neurol, 2000, 42:174-181.)*

- Improved "problem-solving" on means-end task

*(Willatts et al. Lancet, 1996, 352:688-91.)*

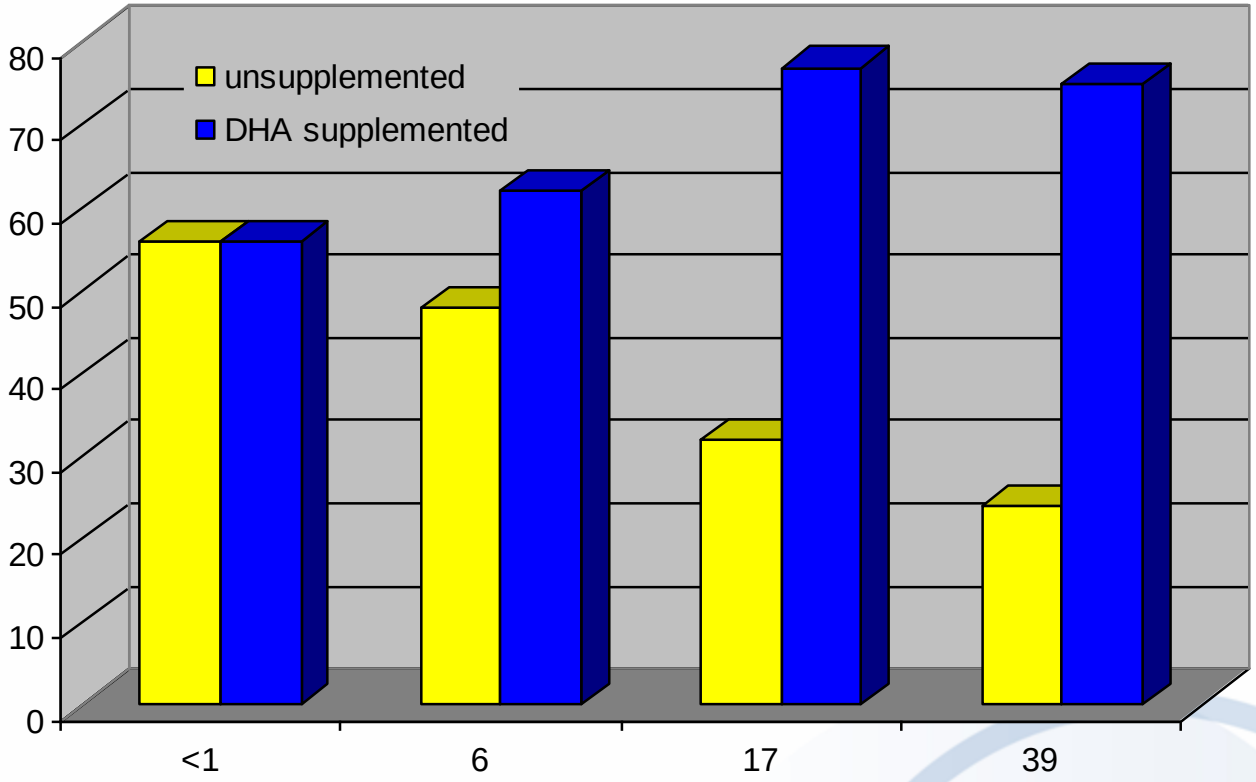
*Current EU expert recommendations promote at least 200 mg DHA/day during pregnancy and nursing
www.perilip.org

# Infants Require a Continued Source of DHA After Birth.

The DHA status of an infant declines rapidly without supplementary DHA.

A comparison of infant formulas: 1 supplemented with DHA the other unsupplemented

**RBC-DHA (ug/ml)**




**Age (weeks)**

Hoffman et al,;J Pediatr Gastroenterol Nutr;2000;31: 540-53.

Birch et al.;Am J Clin Nutr; 2005;81:871-9.

# Born at the right time?

## Prematurity

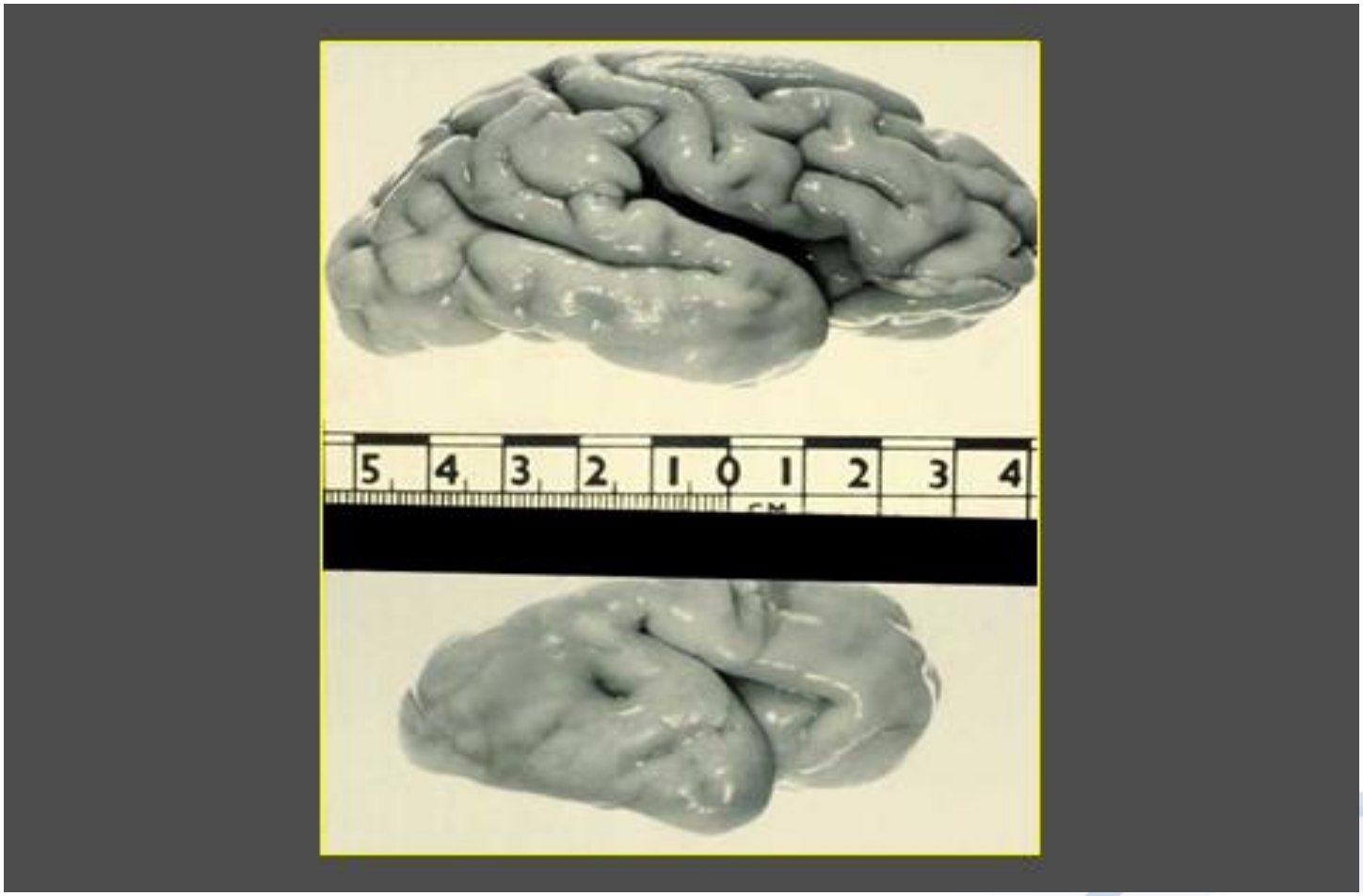
- Interrupts placental DHA transfer and thus may cause **adversely** effect cognitive, motor and visual development.

(Hibbeln et al, Lancet 2007; 73(2): 316-322)

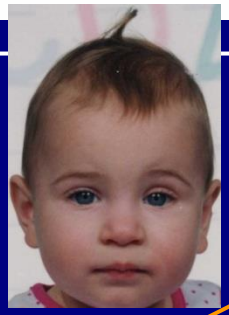
## Full term

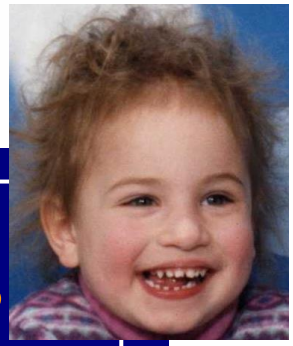
- If mothers have high blood plasma DHA levels then the infants exhibit:
- Advanced eye co-ordination
- Advanced hand co-ordination
- Advanced neurocognitive development (e.g. Helland et al 2008 Pediatrics 2008; 122(2)e472-2479 and Pediatrics 2003; 111(1):e39-e44)

# Brain Growth Age 1 to 5



# DHA Accumulates in the Brain Early and Rapidly







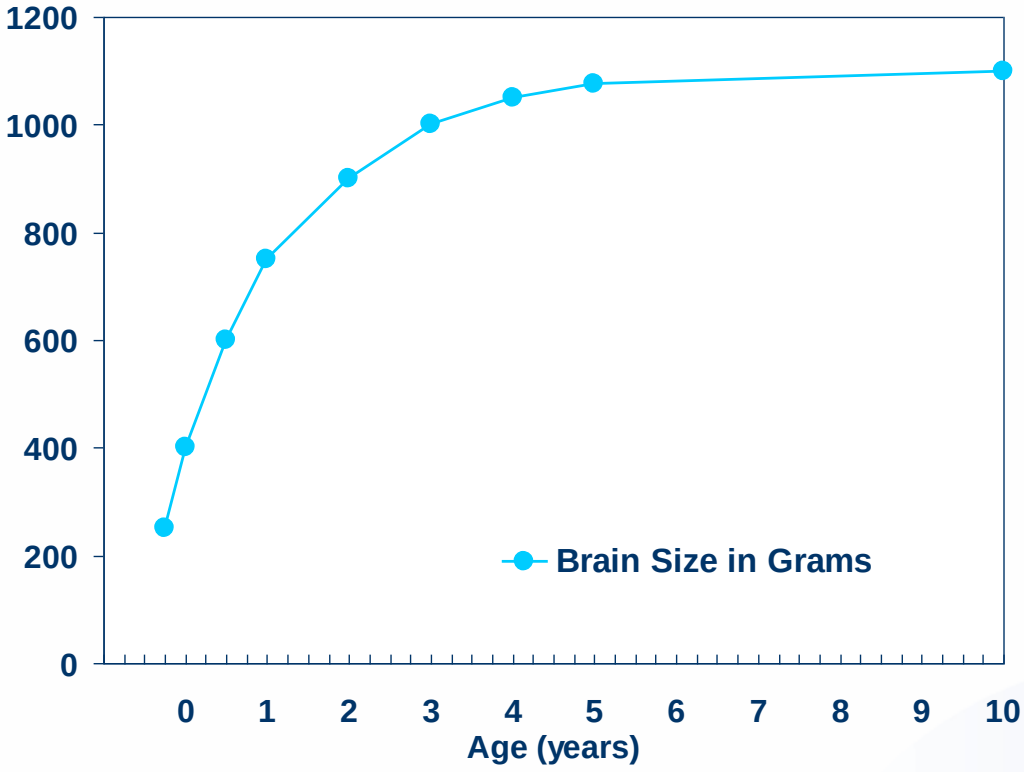

Martinez M. *J Pediatr.* 1992;120(suppl):S129-S138

Brenna T 2008 Workshop on DHA as a Required Nutrient.

# Brain Growth

## Rapid growth from 3rd trimester to 2nd birthday

from birth to one year the brain increases 10-fold in size

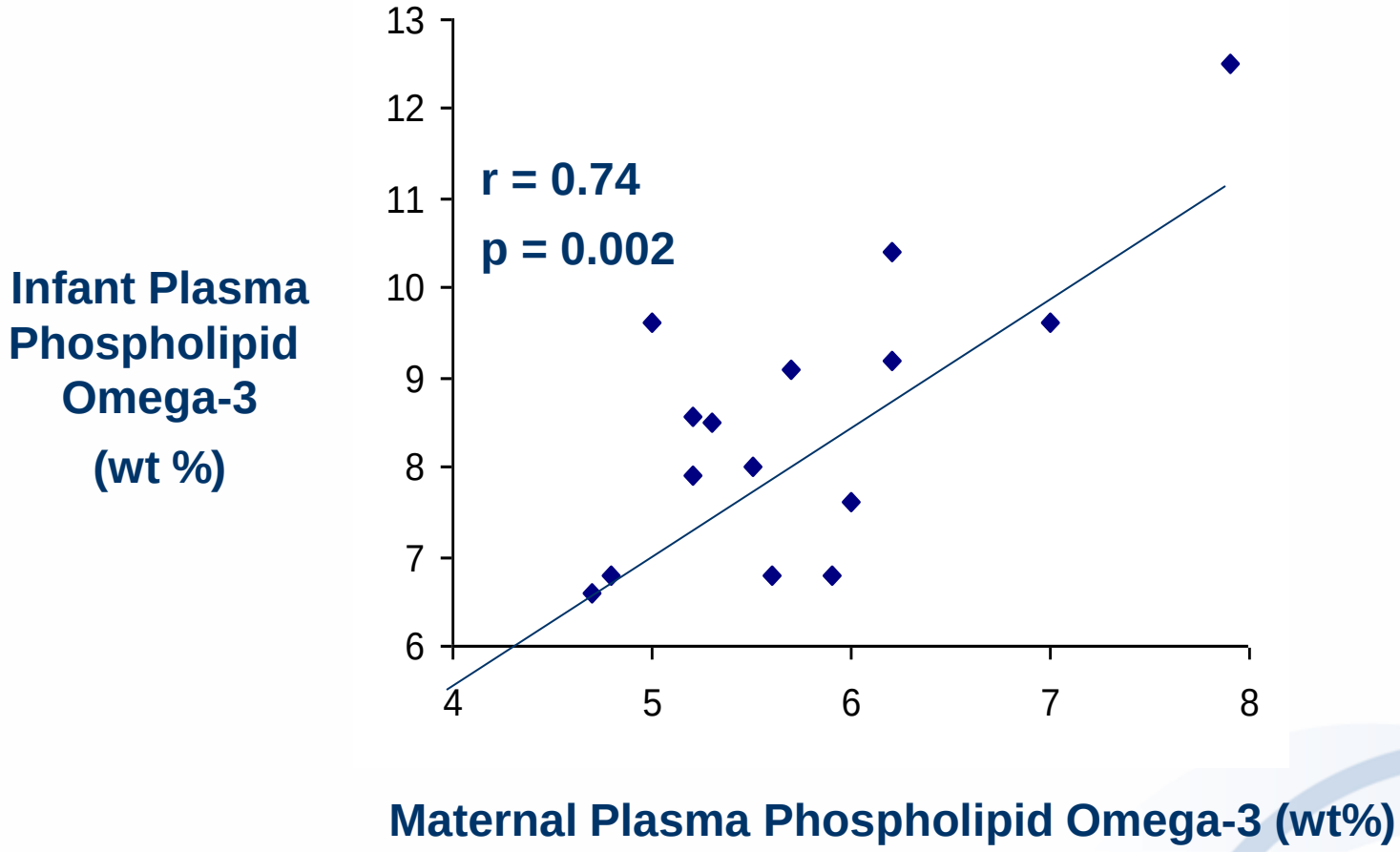



*Dobbing & Sands, Early Hum Dev. 1979*

# DHA in Infant brain development

- DHA has **convincing** benefits for brain (and visual) development in infants (FAO/WHO 2008)
- During gestation, DHA is preferentially transferred across the placenta to the developing foetus.
- The presence of DHA in breast milk is often cited as a possible reason why breast fed babies have superior cognitive function over infants fed with formula NOT supplemented with DHA
  (Laurentzen et al.,Prog Lipid Res (2001) 40: 1- 94)

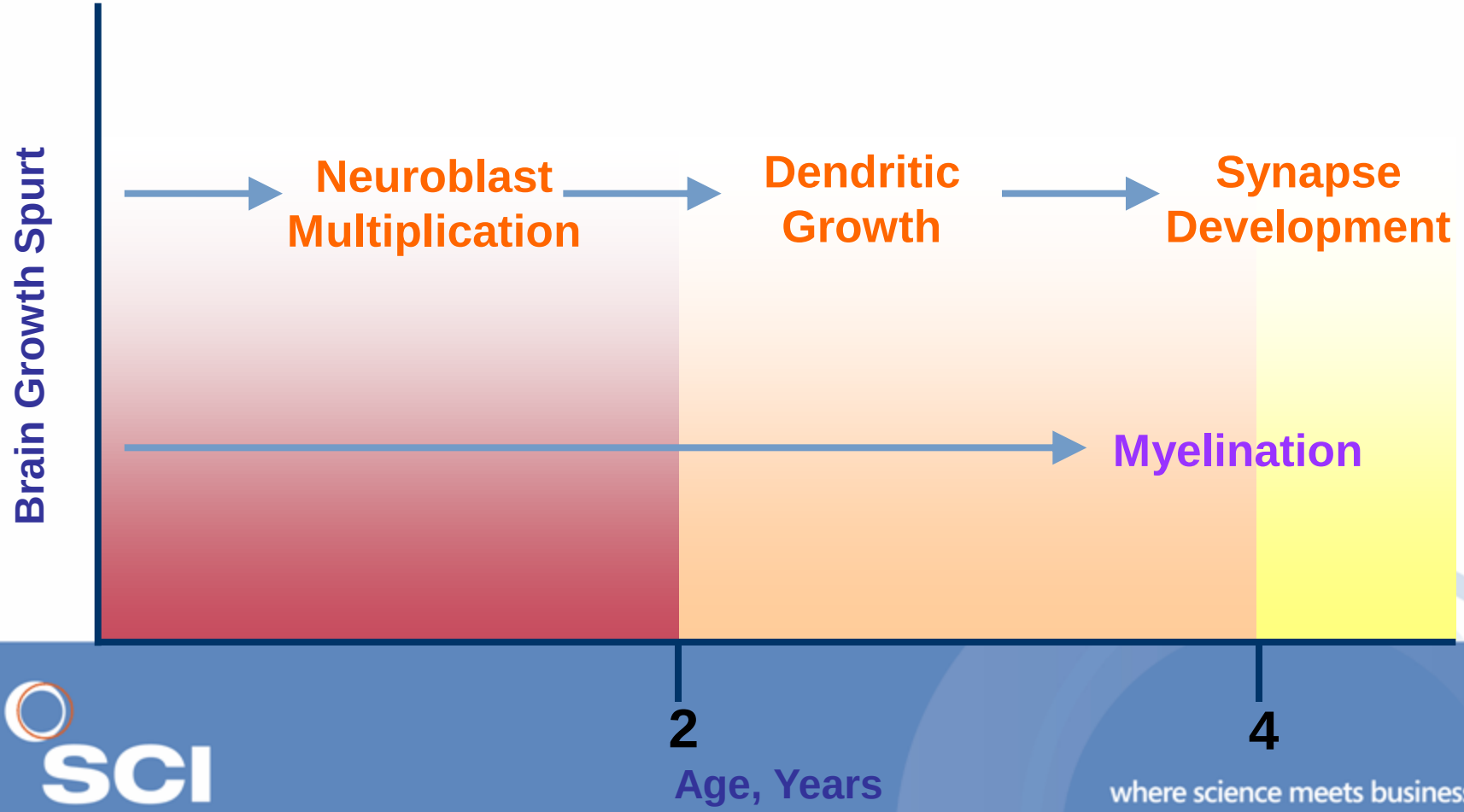
# Maternal omega-3 status determines infant status



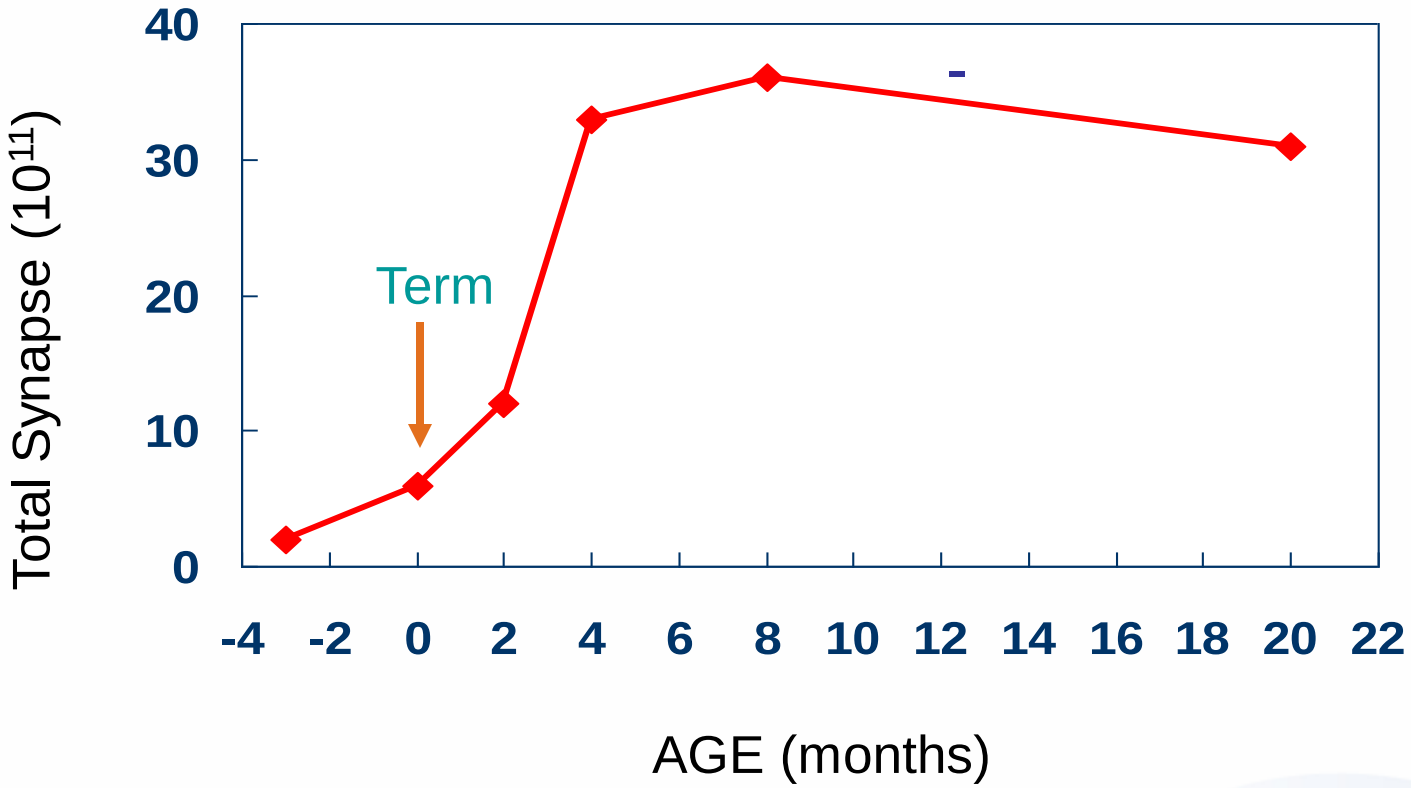



*Al et al, Early Human Develop 1990; 24:239-48*

# Brain Development



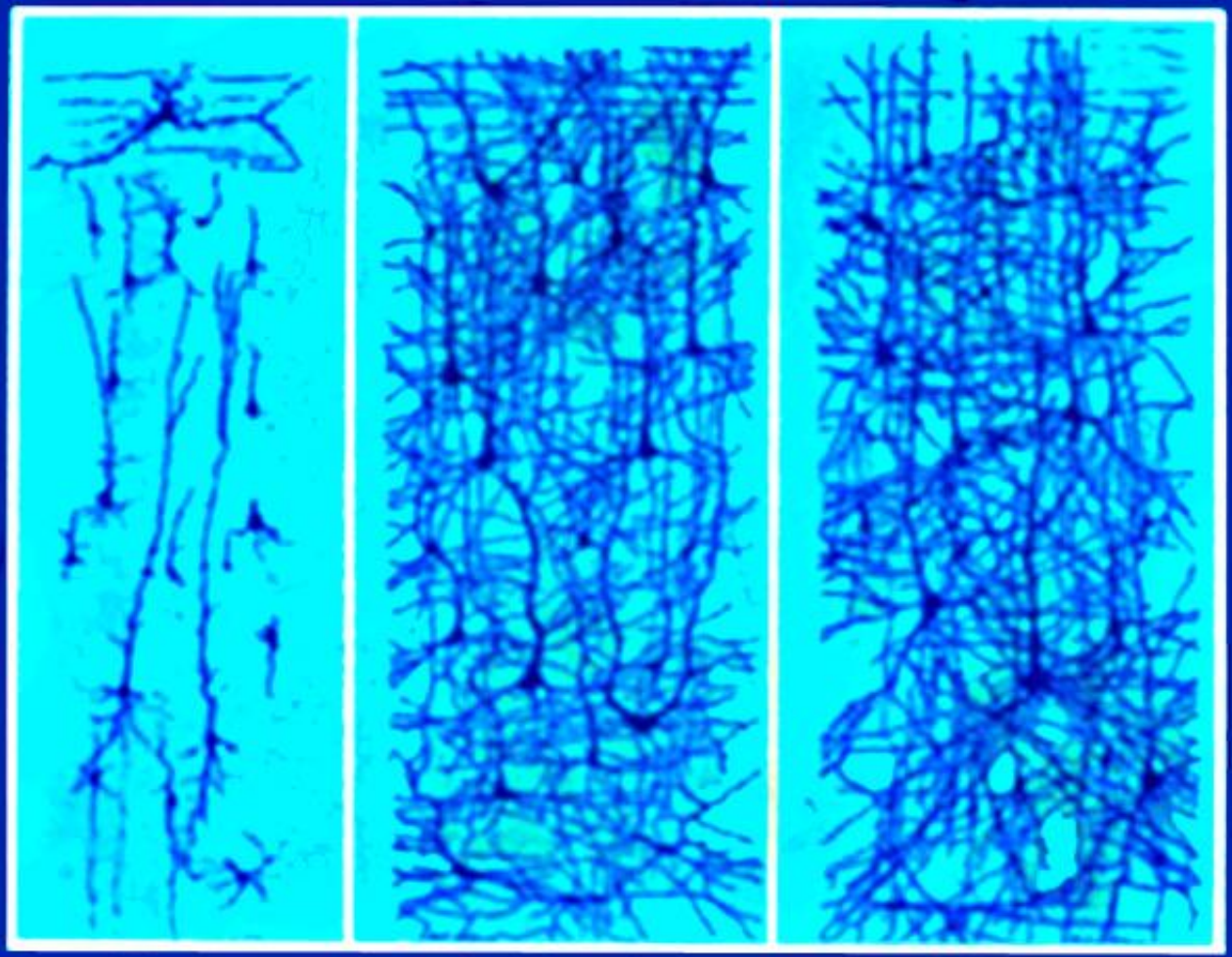
# Development of Neural Synapses in Human Cortex




**From midgestation on, there is rapid synaptogenesis & myelination (50x)**

Huttenlocher & deCourten, *Human Neurobiol* 1987

# POSTNATAL DEVELOPMENT - DENDRITIC TREE



Birth 15 Months 2 Years

Dobbing J, Early Human Devel 3-79-83, 1979

# Toddlers: A preformed source of DHA and ARA is necessary to meet needs

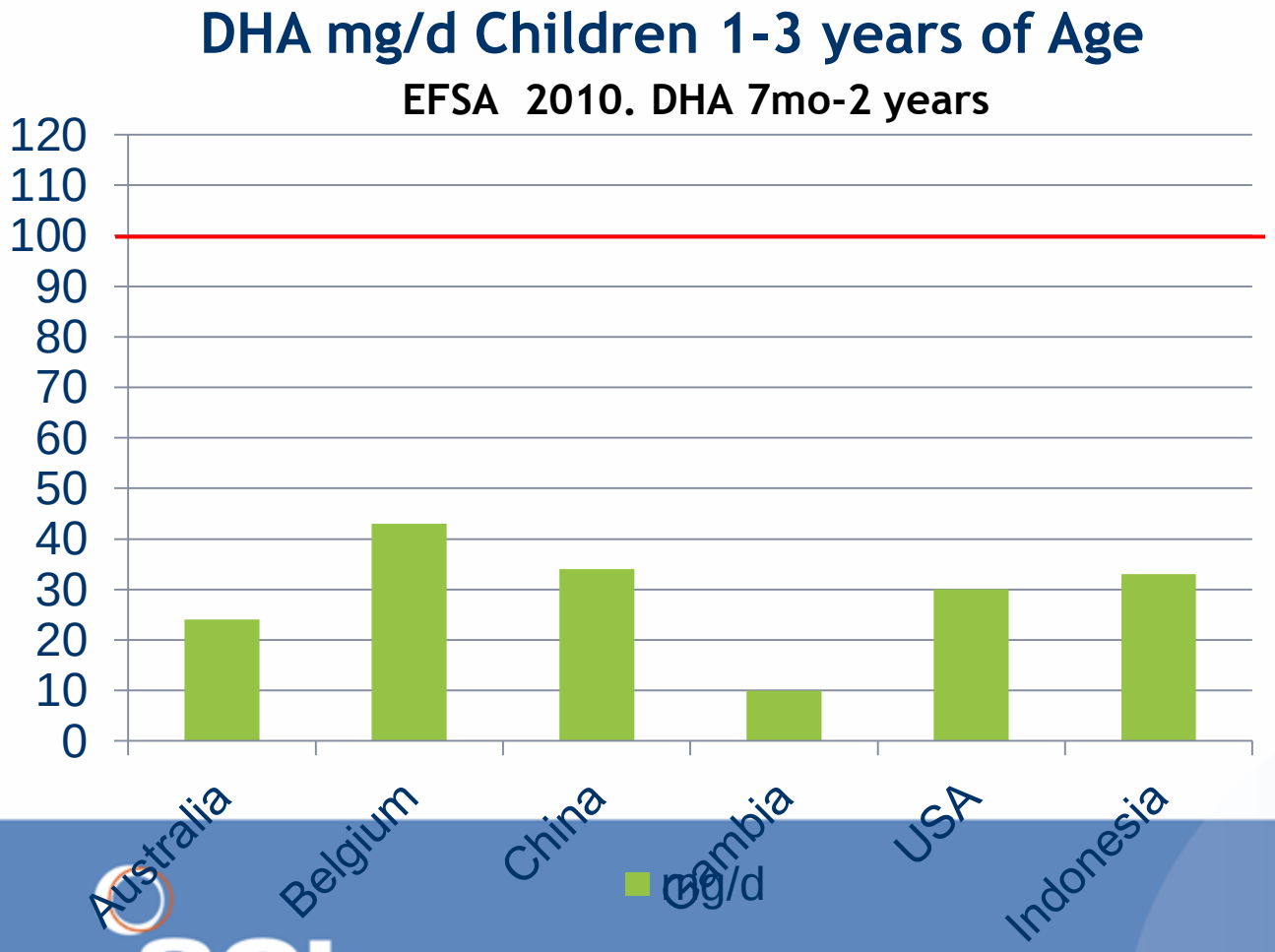
- **Precursors do not convert adequately**
  - By 7 months of age the endogenous synthetic capacity for DHA and ARA declines dramatically from that at birth. (Carnielli, 2007)
  - Preformed LA and ARA are needed to maintain plasma concentrations. (Pawlosky, 2006)
  - In adults changes in dietary LA content do not impact ARA status. (Rett, 2011)
- **Dietary intakes are often inadequate**
  - Complementary foods provide insufficient DHA and ARA to compensate for declining breast milk intake.

# The importance of DHA and ARA in infancy and early childhood: Recent study

- **Long term benefits**

  Infants that consumed formula with DHA+ARA through the first 12 months of life had improved performance on several assessments of cognitive function and on verbal measures derived from standardized tests at 5 years of age (PPVT-111) and 6 years of age (WPPSI-111) *(Colombo 2013; Am J Clin Nutr:98:403-12)*

# DHA Intake During Early Childhood Falls Below EFSA Recommendation




Countries estimated to have the lowest percentage of energy from n-3 fatty acids[1]:

- Burkina Faso
- Ethiopia
- Ghana
- Malawi
- Vietnam

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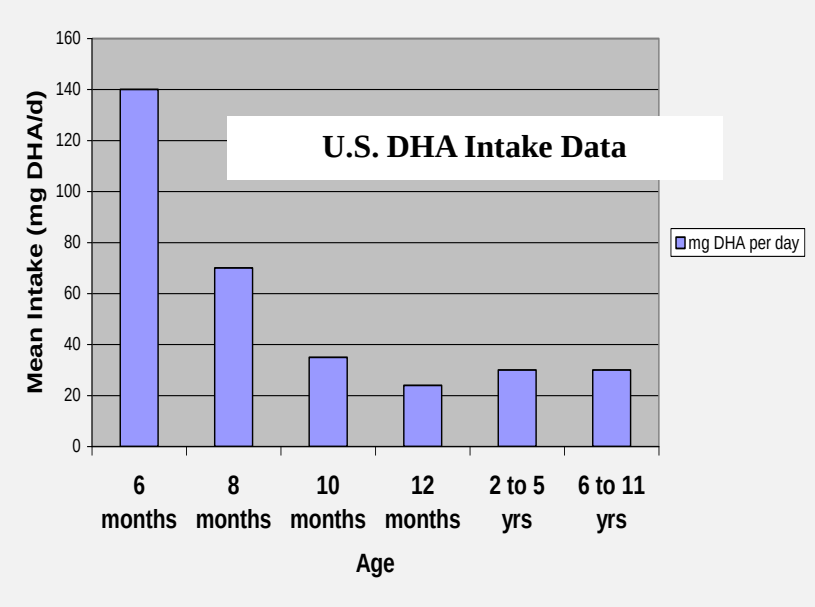
where science meets business

[1]Michaelsen 2011

# Dietary Intake of DHA By Children

- DHA intake decreases during weaning as supplemented infant formula and breastfeeding amounts decline during this time.
- Estimated usual DHA intake in U.S. children 2 to 11 years of age is approximately 20 to 30 mg DHA per day. (NHANES 2009-)
- Typical foods consumed by children are low in DHA. (Makrides 2002)
- Dietary intake of alpha-linolenic acid does not increase blood DHA levels. (Brenna 2009)




Age 2-11 data from What We Eat in America NHANES 2009-2010
Internal data 6-12 months of age.

FAO/WHO Recommendations for EPA/DHA Intake (2010)

100-150 mg age 2-4
150-200 mg age 4-6
200-250 mg age 6-10

US IOM Guidance for EPA/DHA Intake (2005)*

70 mg age 1-3
90 mg age 4-8
100-120 mg age 9-13

* Based on IOM 2005 AI for ALA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# Childhood brain and cognitive function studies

| Ref | Study design | Age yrs | Intervention | Results |
|---|---|---|---|---|
| Perletta 2013 | RCT Cross-over design | 3-13 | 1) 20 weeks *750mg DHA/EPA + 60mg GLA or placebo<br>2) 4 week wash out<br>3) Cross over * | Improved cognitive function –draw a person |
| McNamara 2013 | Observational | 8-10 | H MRS. Comparison of red blood cell DHA to scores Kaufman Brief Intelligence Test, continuous performance task | Higher RBC DHA associated with better reaction time during sustained attention |
| Sheppard 2013 | Observational | 7-9 | 3x24 hour recalls n3 and n6 intake Cognitive function- CANTAB | Higher n-6:n-3 predictive of poorer executive function. Higher n-3 intake predictive of better planning scores |
| Lassek 2011 | Observational-Stepwise regression NHANES III data/ cognitive function | 6-16 | NHANES III-nutrient analysis 40 nutrients including n-3 and n-6 fatty acids. Math and reading tests from the Wide Range Achievement Test-R, Digit span and block design tests from WISC-R | N-3 fatty acids positively related to cognitive test scores |
| Dalton 2009 | RCT | 7-9 | Approx 127mg n-3 LCPUFA/d as a spread for bread versus placebo x 6 mo | Improved verbal learning (HVLTR) and memory |
| Ryan 2008 | RCT | 4 | 400mg DHA vs. placebo x4 mo | DHA in whole blood positively associated with scores on the Peabody Picture Vocabulary Test (p = 0.18) |

# Cheatham C. et al., 2011

- “Fish Oil Supplementation during lactation: Effects on Cognition and Behaviour at 7 years of age”
- A cohort of 122 Danish mothers were supplemented with 1.5g per day EPA + DHA for the first 4 months of lactation/
- The children were tested for cognitive abilities at age 7 years.
- Improved Working Memory was significantly correlated with increased DHA intake.

# Lassek W & Gaulin S., 2011

## "Sex differences in the relationship of dietary fatty acids to cognitive measures in American children" Frontiers in Evolutionary Neuroscience 3(5):1-8.

- Premise: As human females must provide DHA for the growth of the unusually brains of their offspring from maternal fat stored during childhood, their need for DHA is much greater than males.
- Cohort of 4000 children from US Third National Health and Nutrition Examination Survey (NHANES III) aged 6 – 16 years.
- Significant positive correlation of Ω3 intake to improved cognitive test, A corresponding negative correlation was observed with Ω6.
- In female children, positive effect of Ω3 twice as strong as in males
- "It seems possible that the high Ω6:Ω3 ratio in the American diet might contribute to the low ranking of American children in International Testing"

# The DHA (Docosahexaenoic Acid) Oxford Learning And Behaviour (DOLAB) Study

UNIVERSITY OF OXFORD

OXFORDSHIRE COUNTY COUNCIL
CHILDREN, YOUNG PEOPLE & FAMILIES
www.oxfordshire.gov.uk

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where science meets business

# The DOLAB Trial – Overview

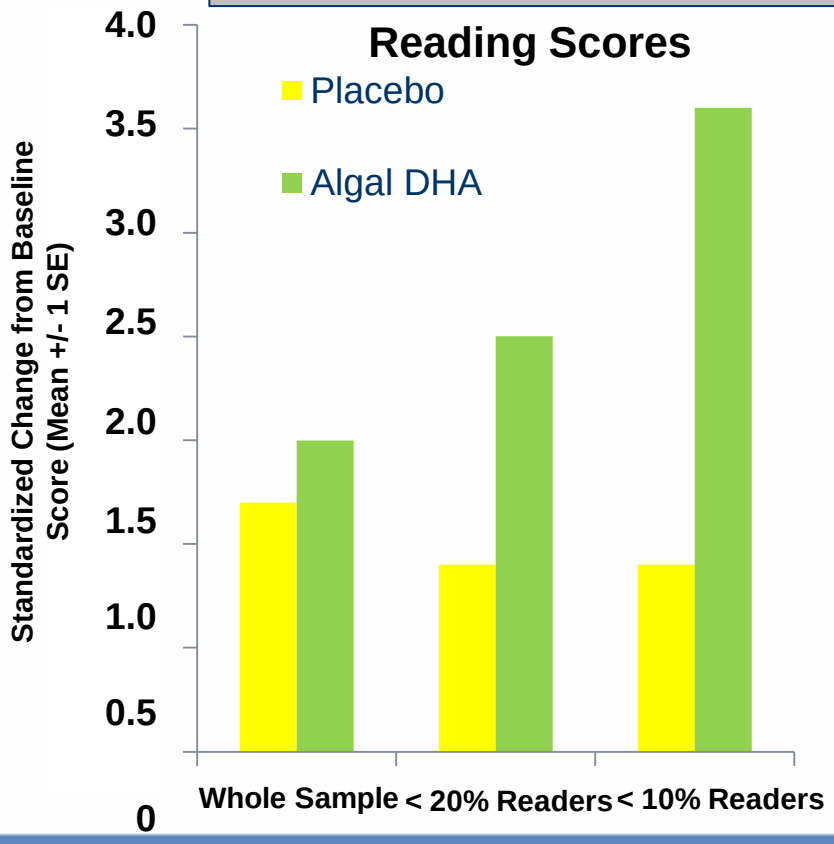
**Richardson *et al*. PLoS One. 2013**

| | |
|---|---|
| **Objective** | To determine the effects of DHA supplementation on reading, working memory, and behavior |
| **Design** | Randomized, double blind, placebo-controlled, parallel group |
| **Setting** | 74 primary schools, Oxfordshire, UK |
| Subjects | Healthy children, aged 7-9 years, underperforming (< 33$^{rd}$ percentile) in reading (n = 362) |
| **Intervention** | 600 mg algal DHA/day or placebo (corn/soy) for 16 weeks |
| **Outcomes** | Age standardized measures of reading and working memory, and parent/teacher rated behavior measured at baseline and after 16 weeks of supplementation |

# The DOLAB Trial – Results

Richardson *et al*. *PLoS-ONE*. 2012

## DHA supplementation improved reading and behavior in children with low baseline reading scores (600mg DHA x 16 weeks)




- Higher blood DHA levels were associated with **better reading**, **working memory**, and parent-rated behavior
- DHA supplementation improved reading in children with baseline reading scores <20$^{th}$ and <10$^{th}$ percentiles, but not in the total study population (<33$^{rd}$ percentile)
- DHA supplementation led to an additional **2 month gain in reading age** in children with baseline reading scores <10$^{th}$ percentile
- DHA supplementation led to an additional **1 month gain in reading age** in children with baseline reading scores <20$^{th}$ percentile
- DHA supplementation improved parent-rated behavior

# DOLAB: The Docosahexaenoic (DHA) Oxford Learning and Behavior Trial

Montgomery P et al., J Sleep Res 2014; 4:364-388.

MicroMini-Motionlogger® , Ambulatory Monitoring Inc.

- The following improvements in Objective sleep were noticed in the children supplemented for 16 weeks with 600mg/day algal DHA in comparison with the placebo group.
- The children slept on average 58 minutes more per night*
- The children were on average 44 minutes less awake during the night*
- There was an 8% improvement in sleep efficiency (i.e. sleep during time in bed)
- Children had on average 7 fewer wake episodes (i.e. brief wakings)
- No significant differences in Subjective Sleep (CSHQ) were noticed by the parents when measured using a Total Sleep Disturbance score derived from a questionnaire given to the parents.
- However, in post-hoc analysis on the subset of children who had previously reported sleep disturbance, there was a significantly lower CSHQ score, demonstrating improved sleep patterns in this group of children.

# Emerging Science:
# Omega-3 status may be linked to sleep quality

**Sleep has well-documented effects on memory and cognitive performance in children**

*Bouke. Sleep Med 2011; Kopasz. Sleep Med Rev 2010; Dewald. Sleep Med Rev 2010)*

## EPIDEMIOLOGICAL STUDIES

- Fewer sleep problems reported in infants and children with higher n-3 fatty acid levels
  *(Papandreou. J Sleep Res 2013)*
- Fewer sleep problems in children with ADHD with higher plasma n-3 fatty acid levels
  *(Burgess. AM J Clin Nutr 2000)*
- Higher maternal plasma DHA during pregnancy is associated with a more mature neonatal sleep-state patterning in the newborn.
  *(Cheraku. AM J Clin Nutr 2002)*

## INTERVENTION STUDIES

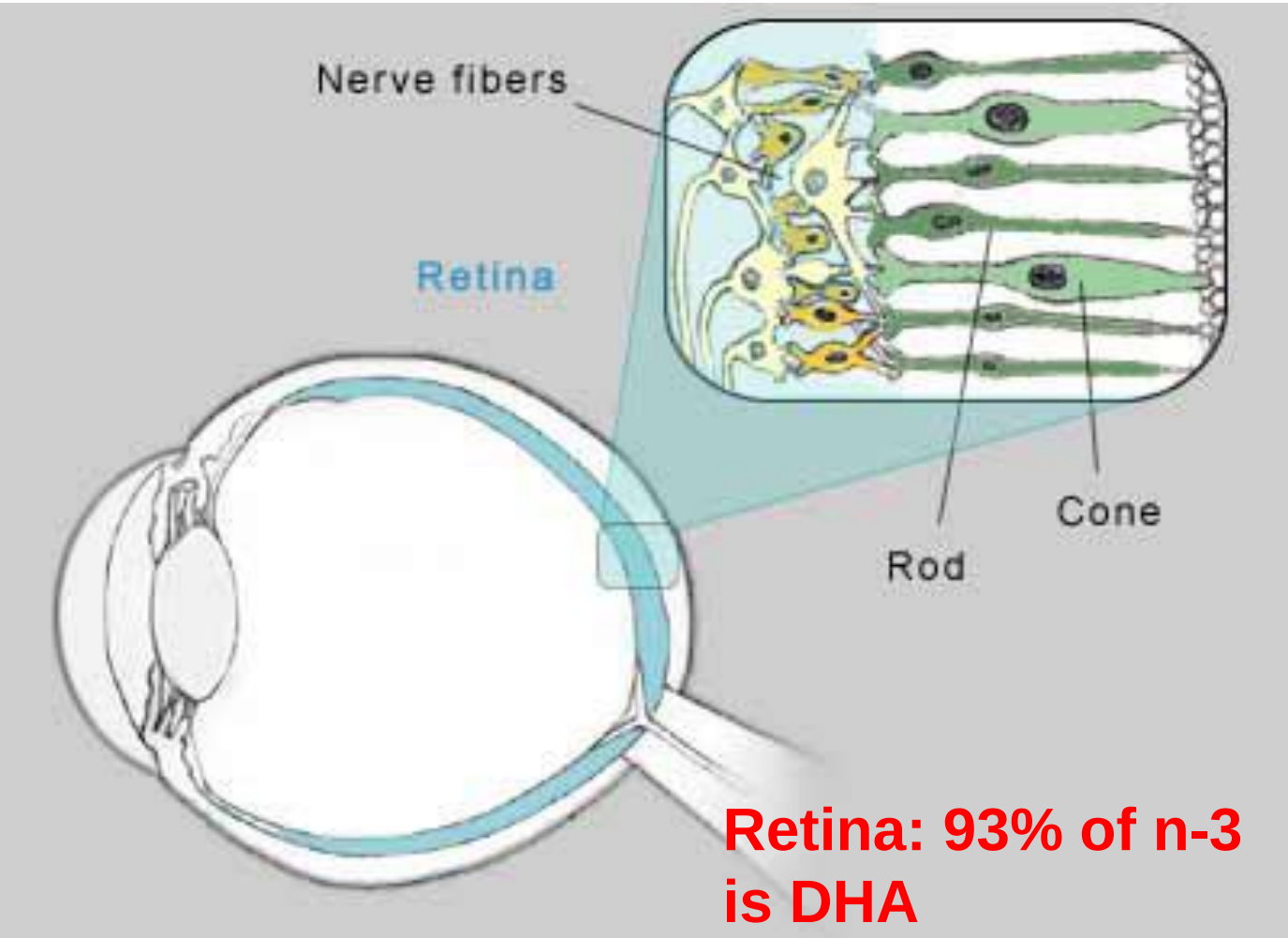
- The prenatal supply of dietary DHA (300mg) has a beneficial impact on infant sleep organization
  *(Judge. Early Human Dev 2012)*
- Improvement in sleep in children (age 5-10) with ADHD, supplemented with 440mg EPA+DHA (+GLA, MG, Zn) x 3 months *(Huss. Lipids Health Dis 2010)*
- **58 minutes more sleep at night in 362 healthy children 7-9 years age 600mg DHA x 4 months**
  *(Montgomery. J Sleep Res 2014)*

# DHA activates the frontal cortex of the brain in boys

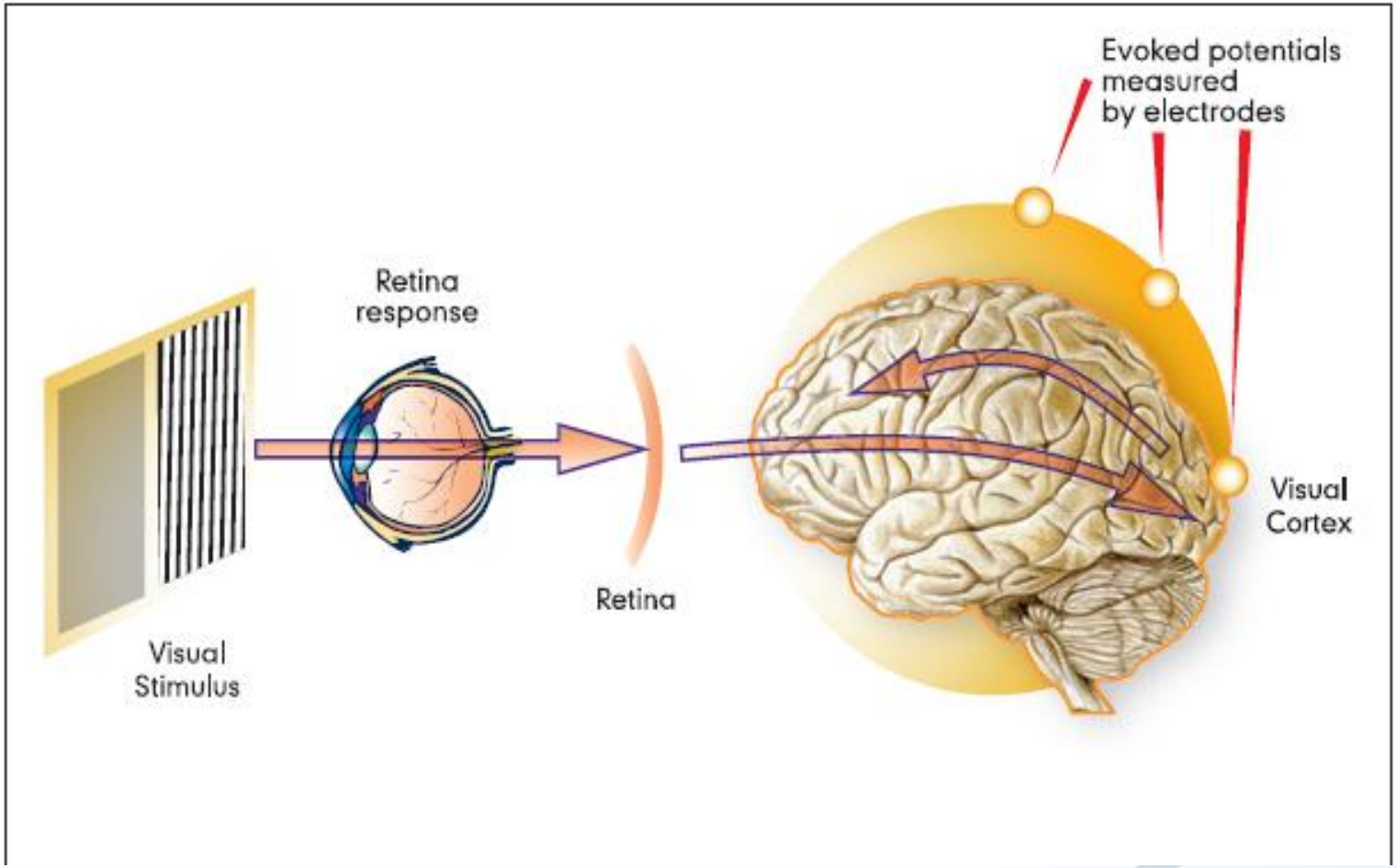
- **DHA supplementation increases prefrontal cortex activation during sustained attention in healthy boys:a placebo-controlled, dose-ranging, fMRI study** (McNamara R, 2010) 2010.Am J Clin Nutr)

# DHA and eye development

# DHA in the Eye: Structure

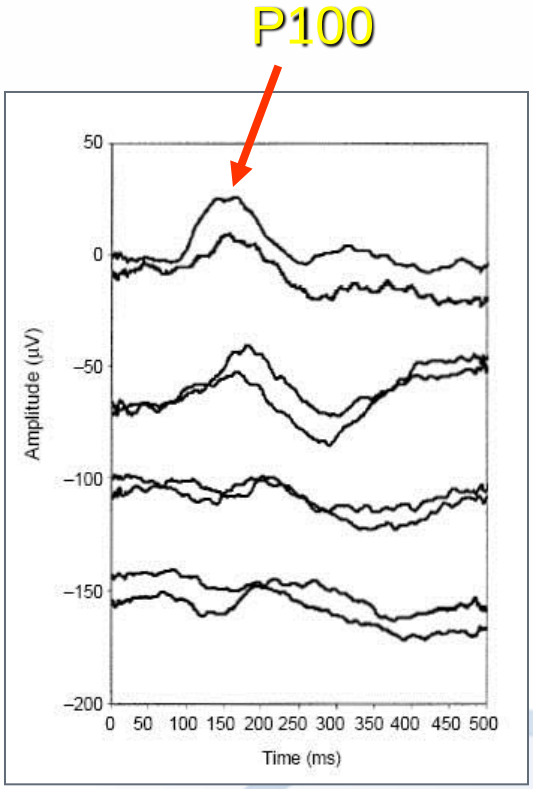


# DHA in the Eye: Structure & Function

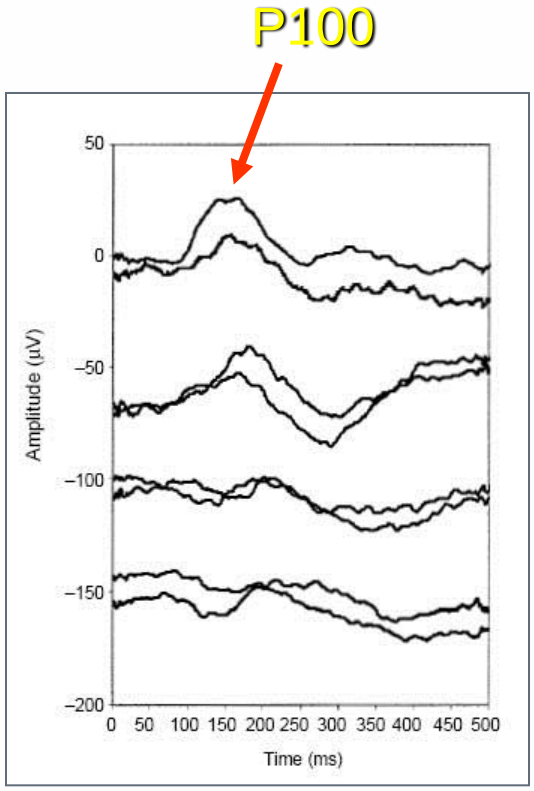


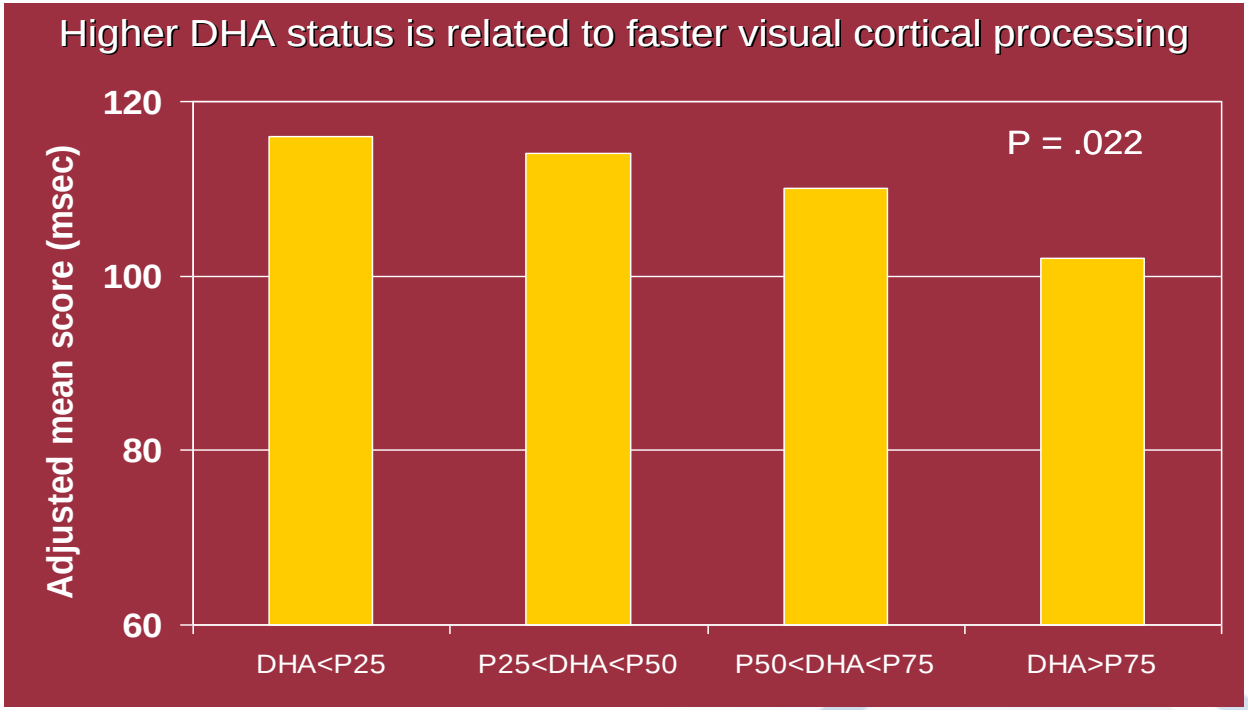

**Measuring visual function**

# Measuring VEP P100 Latency



# Infant DHA At Birth Is Related To VEP P100 Latency At 8 Years



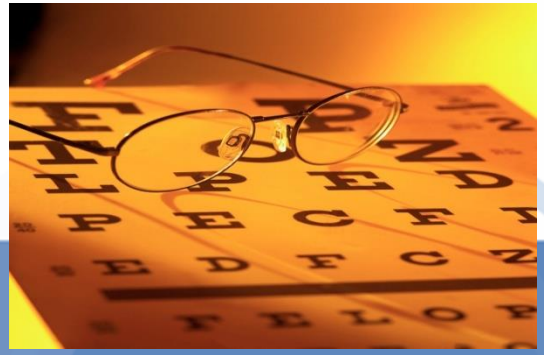

***Bakker et al, 2002***

# DHA /ARA Levels and Visual Acuity

| | %DHA/ARA | Duration | Improved Outcome |
|---|---|---|---|
| Birch ’98 (Birch ’07) | 0.36*/0.72 | 0-4mo | Improved vision at 1.5,4,12,18m. Improved vision at 4yr |
| Birch ‘02 | 0.36/0.72 | 6wk-12mo | Improved vision at 4,6,12mo |
| Hoffman ‘03 | 0.36/0.72 | 4/6m-12m | Improved vision at 12mo |
| Hoffman ‘04 | 108mg -food | 6m-12m | Improved vision at 12mo (1.5 lines on eye chart) |
| Birch ‘05 | 0.36/0.72 | 0-12mo | Improved vision at 4,9,12mo |
| Makrides ‘95 | 0.36/0.1 | 0-7.5mo | Improved vision at 4,7.5mo |

Infants aged 0-6 months consume 100-140mg DHA/day

*18mg/dL; **8mg/dL



# Birch et al, 2010, DIAMOND study

- "The DIAMOND (DHA Intake And Measurement Of Neural Development) Study: a double-masked, randomized controlled clinical trial of the maturation of infant visual acuity as a function of the dietary level of docohexaenoic acid", Am J Clin Nutr 2010; 91: 848-59.

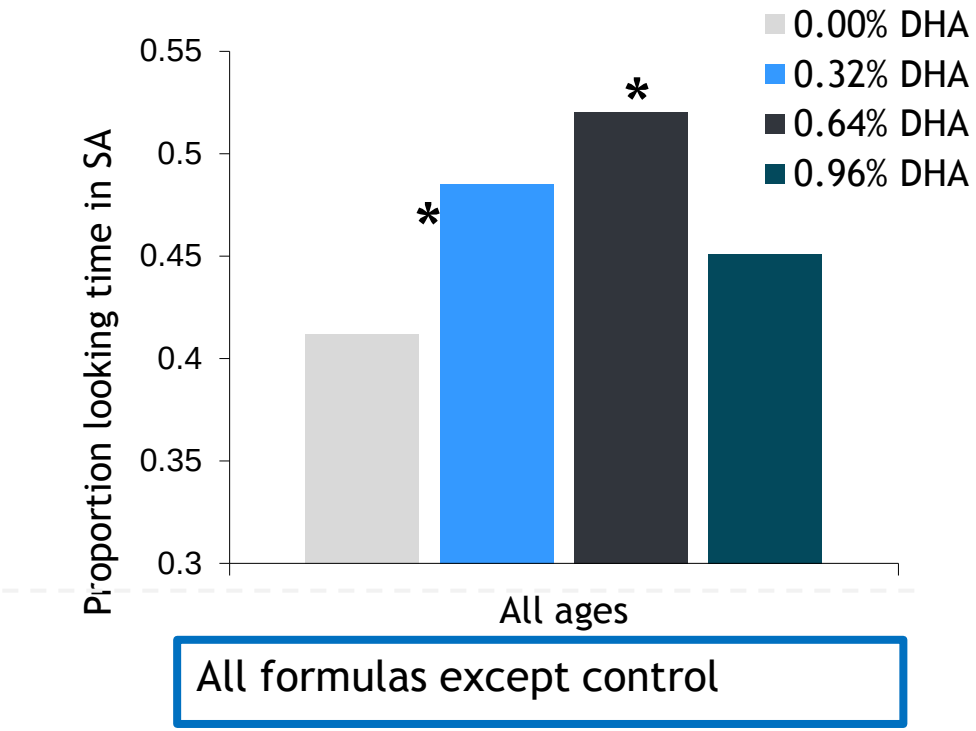
- 343 healthy term babies were fed formula with 4 levels of DHA: 0, 0.32%, 0.64% and 0.96%. (The formula also contained 0.64% ARA).

- Visual Evoked Potential was measured at 12 months. All supplemented groups performed better than the controlled group, but there was not significant difference between the 3 groups.

- **The study confirms that a level of 0.32% DHA is infant formula is sufficient to improve a child's visual acuity.**

# DIAMOND TRIAL: Sustained Attention

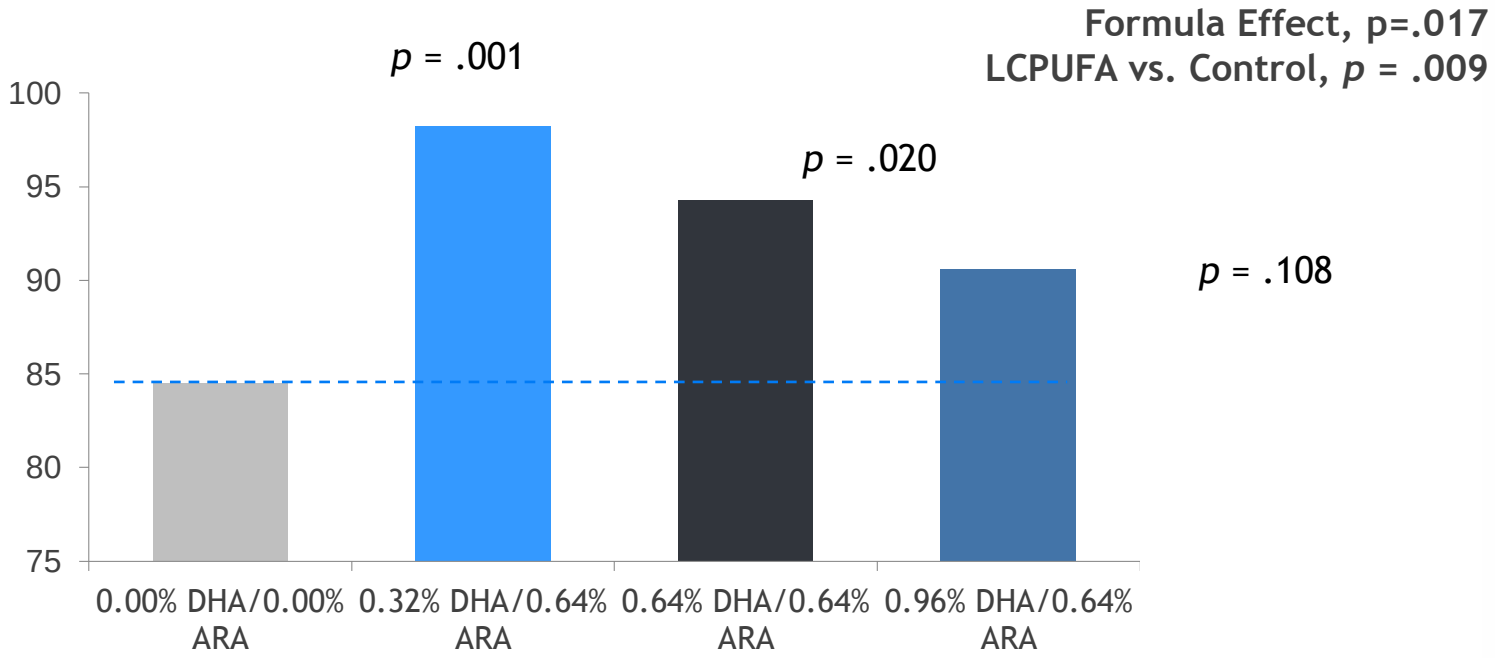
## *Cognitive Benefits of DHA lost when DHA exceeds ARA level*




Colombo et al., *Ped Res,* 2011, 70:406-10

# THE DIAMOND TRIAL:5-YEAR VERBAL IQ

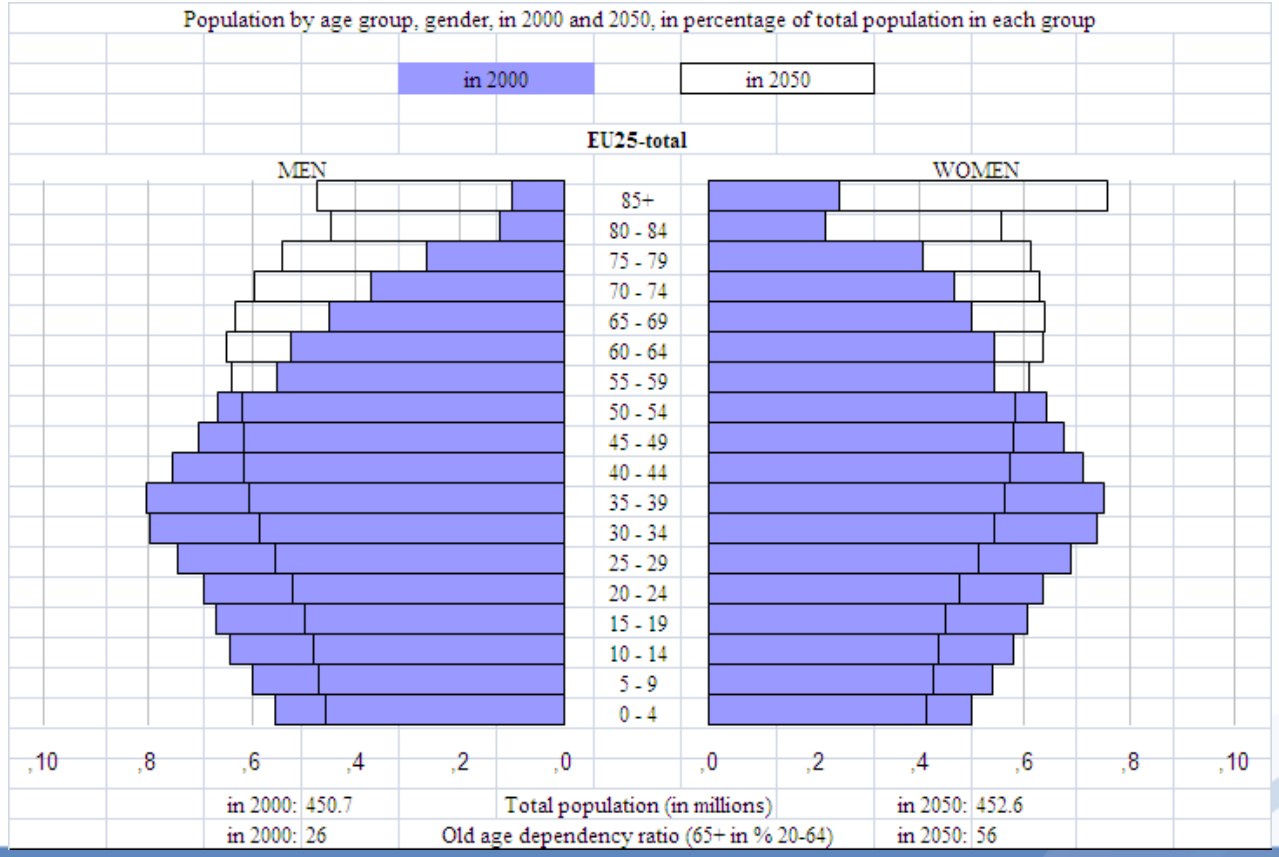
Peabody Picture Vocabulary Test: Standardized Score at 5 years




Colombo et al . AJCN, 2013 98: 403-412

# The impact of DHA supplementation on age-related cognitive decline

# Europe's population will get older



# How big is the problem?

*“Our estimate is that more than 6 million Europeans are affected by different types of dementias. If we consider the fact that in most cases it is families and relatives who are caring for those patients, then we can estimate that more than 19 million people in Europe experience the devastating consequences of dementias every day.”*

Androulla Vassiliou, European Commissioner for Health, from her speech during "The fight against Alzheimer's and related diseases" conference, Paris, 31 October 2008

# The Dementia Explosion

- The worldwide cost for dementia will reach USD 604 billion (Euro 435 billion) in 2010
- The number of sufferers will TRIPLE by 2050
- 35.6 Million people currently suffer from Alzheimer's disease
- Whilst the problem is mainly in the developed world, it will spread rapidly to developing countries

Source: Alzheimer's Disease International (as reported in Reuters on 21.9.2010)

# DHA and the Aging Brain

*Background on Aging, Alzheimer's, and Age-related Cognitive Decline*

- Brain DHA is dependent on dietary intake
- Low brain and blood DHA status is associated with Alzheimer's Disease
- Higher DHA dietary intake is associated with significantly reduced risk of AD
- Spatial memory tasks are dependent on DHA in rats
- DHA oxylipin derivatives (NPD1) are neuroprotective
- Transgenic animal models show DHA reduces amyloid and tau (decreased plaque and behavioral deficits in aged Tg2576)

# OPAL Study

## Dangour et al, 2010, April, Am J Clin Nutr.

A double blind RCT concerning 798 older people and fish oil supplementation over 24 months conducted in the UK. The participant received 700mg/day of fish oil (500mgDHA, 200mgEPA).

No differences in cognitive function between the intervention and placebo groups were found using the California Verbal Learning Test as the primary endpoint

However:-

- 500mg of DHA per day is low in this context
- Baselines levels of DHA were not determined
- Plasma DHA/EPA was not correlated with cognitive outcome
- The cohort inclusion criteria did not include memory function
- There were no interim cognitive testing time points in the study (Could an effect at 6, 12 or 18 months been missed?)

# MIDAS *Memory Improvement with Docosahexaenoic Acid Study*

Yurko-Mauro, K., et al. (2008). *J of Nutr, Health & Aging* 12(7): 422-425.

Goal: Evaluate the effects of DHA on cognitive outcomes in healthy elderly (≥55 yrs.) with a mild memory complaint (Martek-sponsored study)

## Trial Design

- Randomized, double-blind, placebo-controlled, parallel, multi-center
- Oral Dose: 900 mg/day DHA or placebo (corn/soy) for 6 months.
- 465 subjects with subjective memory complaint
- 1º Endpoint: cognitive test of memory, attention & learning (Cantab™): Paired Associate Learning test (PAL)
- 2º Endpoints: cognitive tests of executive function, Daily Living skills, visual acuity, plasma phospholipid fatty acid levels, safety and tolerability

# MIDAS Study – Results

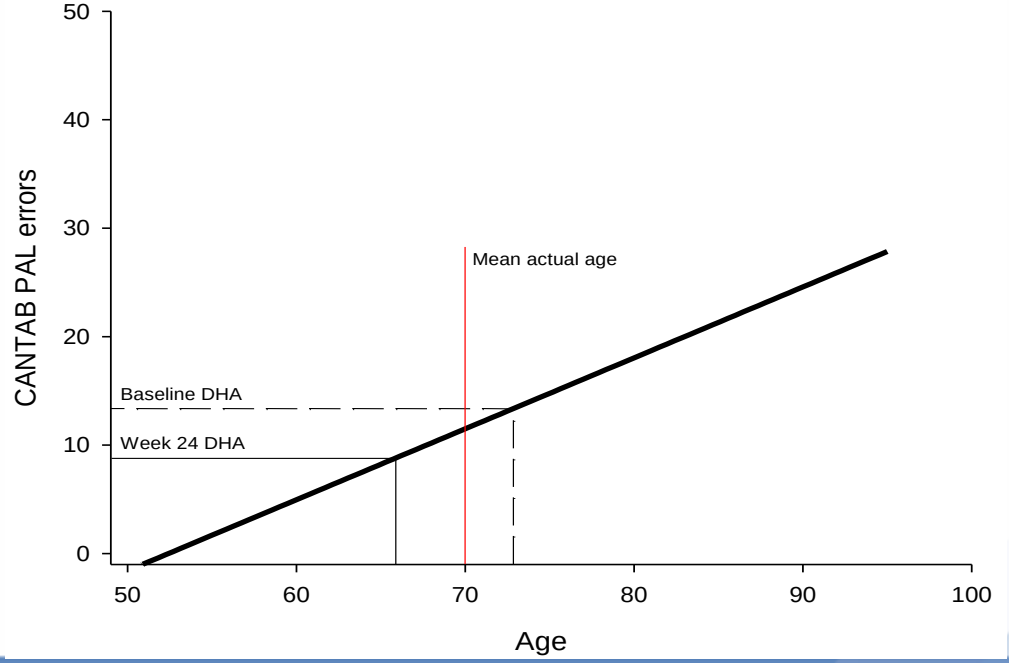
**50% less errors were made on PAL test with DHA treatment**

(LS mean, DHA -4.3+/- 0.61 vs. -2.7 +/- 0.61 placebo, p<0.032, ITT)

- PAL was correlated with plasma DHA levels (p<0.04)
- Verbal Recognition memory test showed significant changes with DHA, p<0.02
- Tests of working memory, executive function did not show improvements with DHA
- No changes in MMSE, Geriatric Depression

# MIDAS Study – Results

Compared to normative data on CANTAB PAL, our results show a 7 year
improvement with DHA versus 3.6 year improvement with placebo. This
represents a change from the 35th to 45th percentile on this test.



# MIDAS – Conclusions

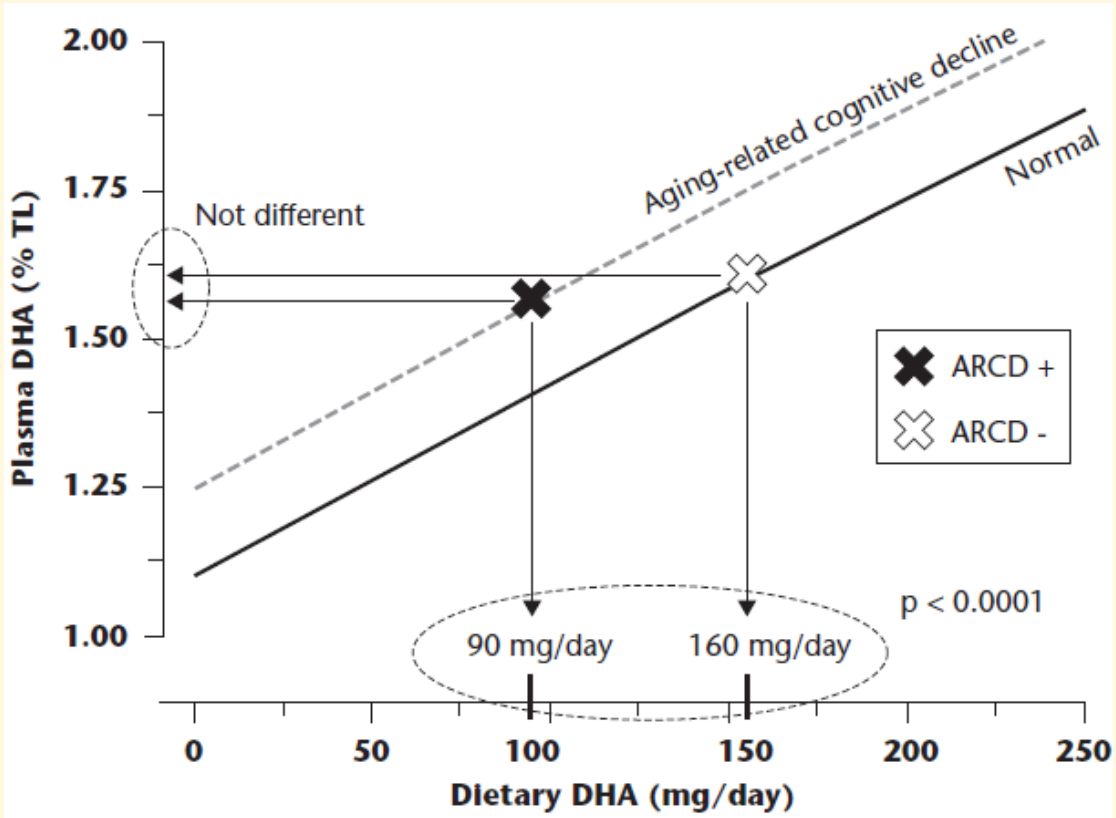
- MIDAS is the first-ever large, randomized and placebo-controlled study demonstrating the benefits of algal DHA in maintaining and improving brain health in older adults.
  - Fish oil (DHA+EPA) studies in this area have shown mixed results.
    - "van de Rest" study, using fish oil containing DHA in comparable amounts to the MIDAS study, found no benefit to fish oil consumption on cognitive performance in healthy aging adults *(Neurology, 2008).*

- *life'sDHA™,* the algal DHA (900mg/d) used in MIDAS, improves learning and memory recall in age-related cognitive decline.

- Algal DHA has a significant impact on early episodic memory changes.

- Algal DHA significantly decreases heart rate in this older population, demonstrating cardiac benefit.

# Dietary v plasma DHA in aging-related cognitive decline (ARCD)




Source: Castellano et al, 2011, OCL 18(4)175-180.

# Meta Analysis of EPA/DHA intake and adult episodic memory 2015

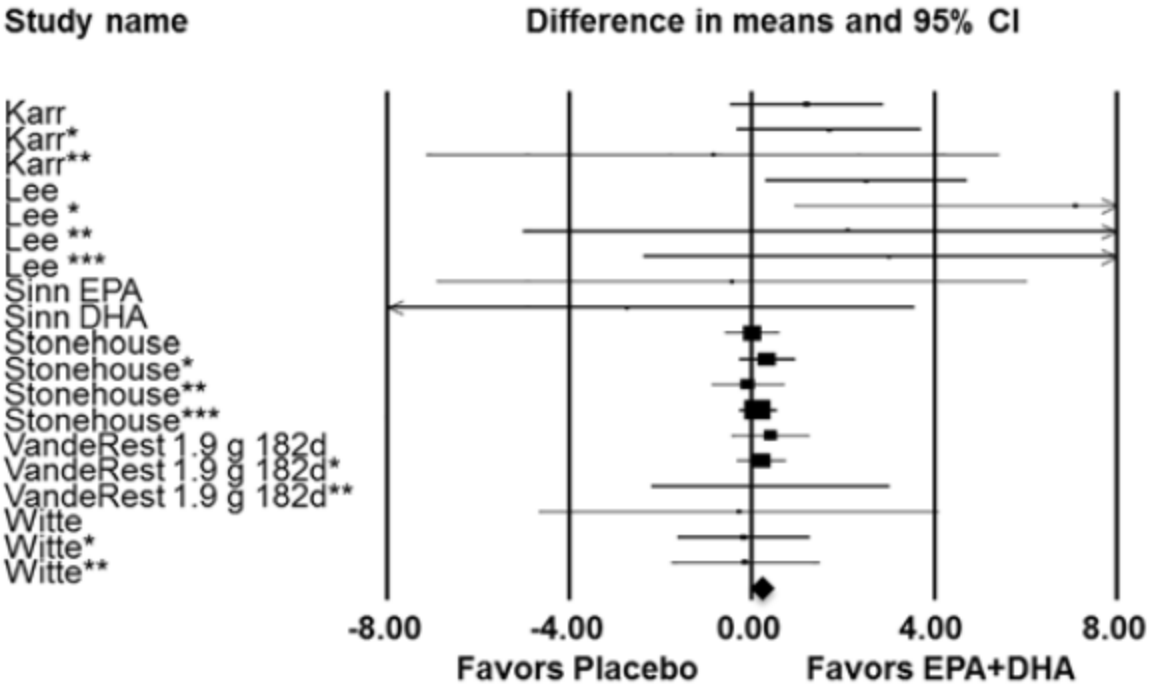



**Fig 3. Forest plot with meta-analysis of dose and episodic memory.** Episodic memory data from pertinent human intervention studies (n = 6) of DHA supplementation alone or in combination with EPA > 1g in all adults. *Asterisks denote study included more than one test of episodic memory, results for each episodic memory test within a given study represented individually. Summary statistics are as follows z = 1.81 (p = 0.070); Hedge's g z = 2.05 (p = 0.04).

Yurko-Mauro, K., Alexander, D. D., & Van Elswyk, M. E. (2015). Docosahexaenoic Acid and Adult Memory: A Systematic Review and Meta-Analysis. *Plos One*, *10*(3), e0120391. http://doi.org/10.1371/journal.pone.0120391

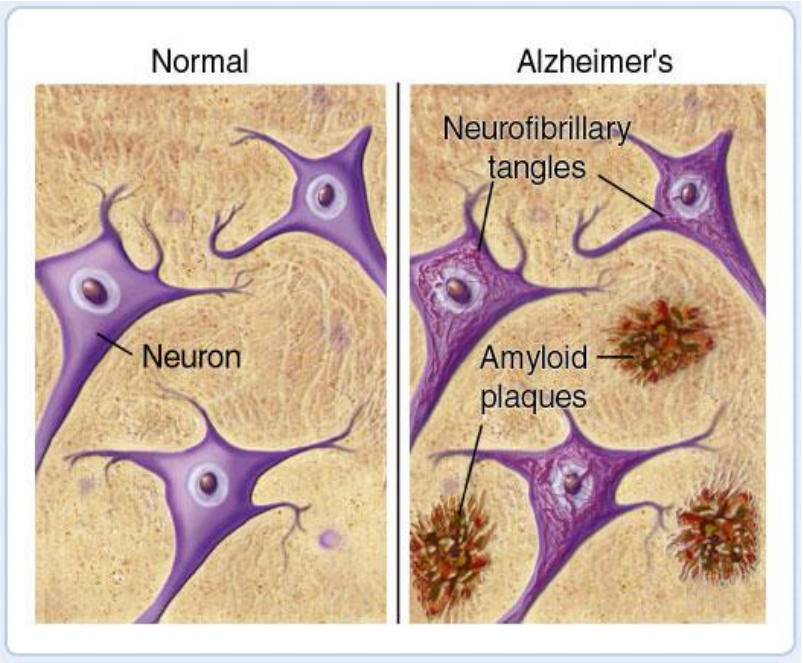
# Alzheimer's Disease

- The most common form of dementia
- A progressive, degenerative, ultimately fatal brain-wasting disease. The symptoms are:
  - Memory loss
  - Disturbed mood
  - Psychosis
  - Depression
  - Loss of linguistic articulation

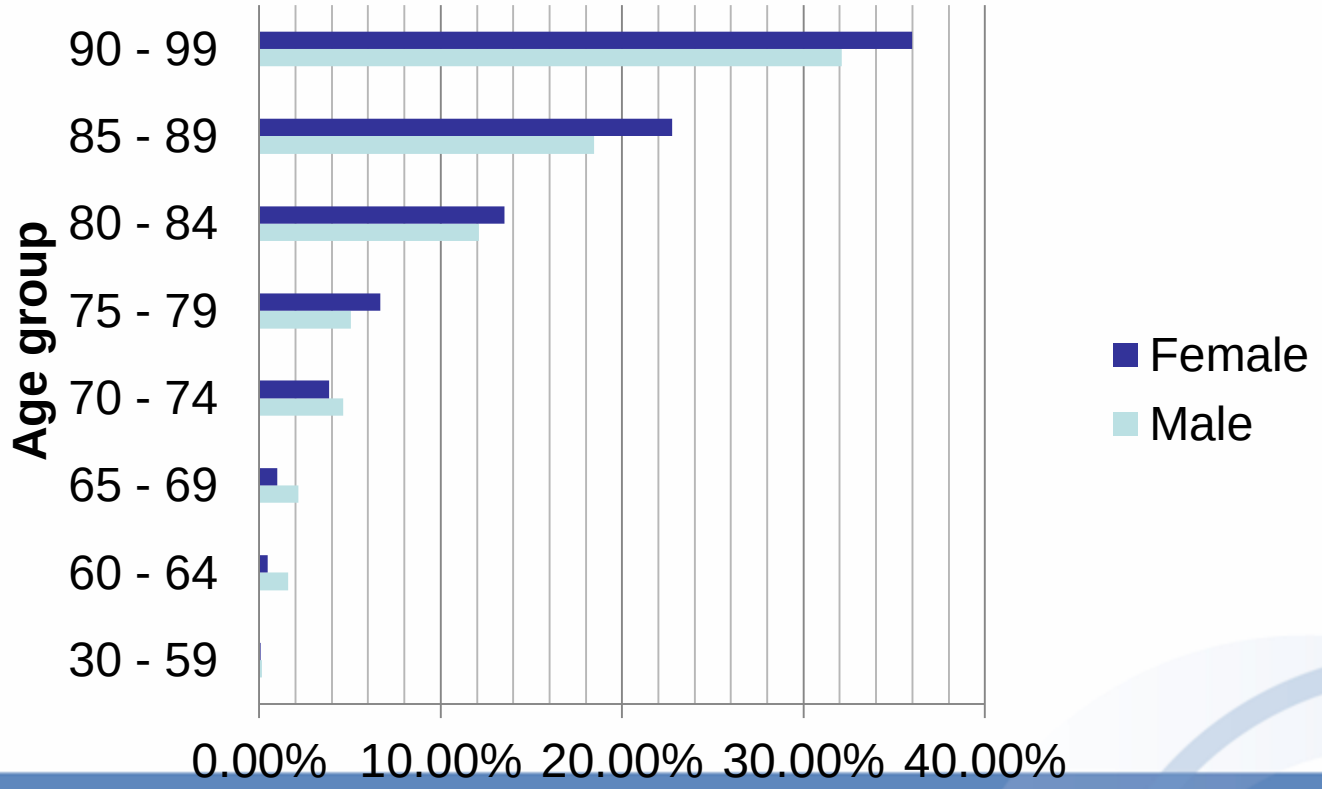
- The main risk factors are age and genetics, but an imbalance of protective factors are also important
- There is no pharmaceutical treatment to halt progression of the condition

# The pathological hallmarks of Alzheimer's Disease

The pathological hallmarks of Alzheimer's are brain lesions consisting of the extracellular accumulation of β-amyloid protein as **amyloid plaques**, and intracellular accumulation of hyperphosphorylated protein Tau in the form of **neurofibrillary tangles.**



# AD EURODEM prevalence rates



# Could the Mediterranean diet offer protection from the onset of AD?

- The Mediterranean diet typically is associated with lower energy density and lower glycaemic index. It is also rich in marine omega 3 fatty acids, B, C and E vitamins, carotenoids and polyphenols.
- Observational studies (including 3C study in France) show that high adherence to a Mediterranean diet is associated with slower cognitive decline. However the possible confounding effect of a more healthy lifestyle must also be considered.
- The ApoE4 allele has a major effect
- DHA and EPA intake was positively associated adherence to the Mediterranean diet, whilst intake of Omega 6 PUFA's was negatively associated. There was no association with land derived Omega 3 fatty acid ALA. (Barberger-Gateau et al, 2011, OCL 18:4:224-7.)

# Marine LC-PUFA's and AD

- Fotuhi et al., 2009. made a meta-analysis of 4 clinical trials and 8 observational studies that used AD or dementia as an end point. They found support for **Omega 3 fatty acids slowing cognitive decline in elderly individuals without dementia**, but not for prevention or treatment of dementia itself. However the authors commented this may be due to the highly divergent study designs. (Fotuhi et al, 2009. Nature Clinical Practice Neurology 5(3)).

- Castellano et al reported using tracer studies that **DHA homostasis is different in the elderly** compared with the young. They comment Apo E4 may contribute to this. This may indicated higher plasma DHA levels are required in the elderly for good health. (Costellano et al, 2011, OCL 18(4):175-180).

- It has been shown that **DHA in the brain is converted to Neuroprotectin D1** (NPD1) in response to oxidative stress and ischaemia-reperfusion (stroke). NPD1 has been shown to be protective of human brain cells exposed to the amyloid-β protein. (Bazan & Asatryan 2011, OCL 18(4): 208-13).

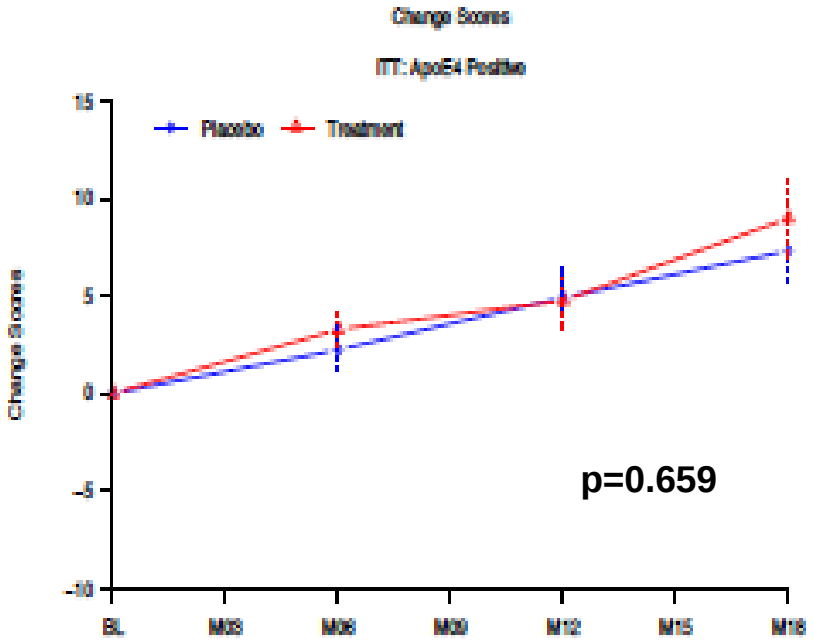
# NIH Trial – Martek DHA for the Treatment of Alzheimer's Disease

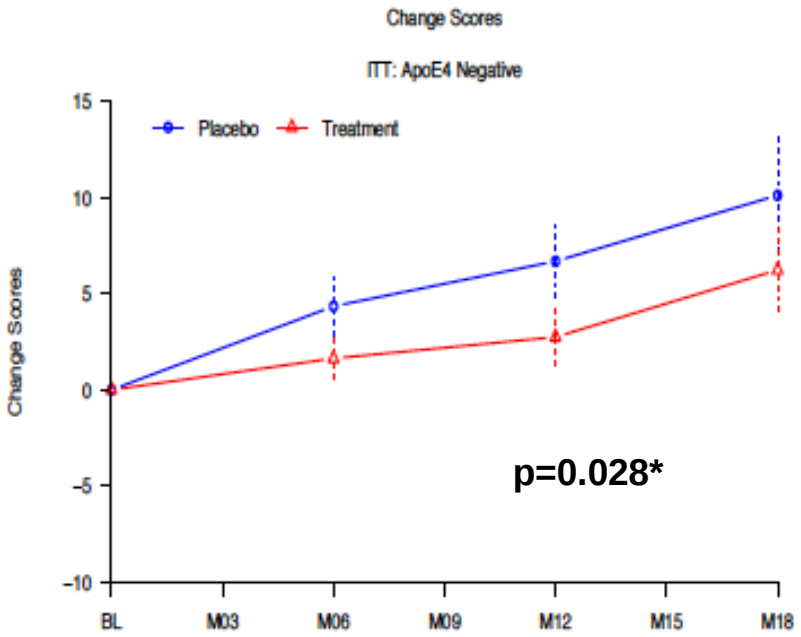
Hypothesis: DHA supplementation will slow the rate of cognitive decline in patients with mild-to-moderate Alzheimer's Disease (AD) by a combination of antioxidant, anti-amyloid, and neuroprotectant effects.

**Trial Design**

- Randomized, double-blind, placebo-controlled, parallel, multi-center study
- Doses: 2,000 mg DHA/day vs. placebo
- Study treatment: 18 months
- Sample size: 400 patients
- Sites: 50 (U.S.) coordinated by ADCS
- Study Timeline: Start: Jan 1, 2007 Complete: 2009
- Primary Endpoint: changes in Cognitive measures: ADAS-Cog and CDR-SOB
- Secondary Endpoints: biomarkers, fatty acid levels, MRI, safety measures

# Pre-specified sub-group analyses: ADAS result in ApoE4 positive and negative




**E4 positive**
**n=135 DHA; n= 94 placebo**

**E4 negative**
**n=91 DHA; n=67 placebo**

***not corrected for multiple comparisons**

# Summary

- Dementia, including Alzheimer's Disease is likely to be fastest growing major health concern of the century
- In the MIDAS trial DHA has been shown to be able to reverse the effects of mild memory impairment in otherwise healthy pensioners.
- The recent NIH study indicates that DHA may be able to improve the cognitive function of AD sufferers who do not have the ApoE E4 allele.

# DHA and Brain Health Summary

- DHA widely acknowledged as important for maintenance of adult brain health. EFSA 13.1 Health Claim for this exists.
- DHA Widely acknowledged as helping adult memory
- EPA rich fish oils have been shown in several meta-analysis to prevent depression
- DHA known to be important in delaying cognitive decline
- DHA may be protective  in the ApoE4 positive elderly in preventing the onset of Alzheimers Disease (Quinn J et al, 2010). Possible combo effect with high dose Vitamin E (Dysken, 2014).
- DHA important in combating traumatic neurological injury.
- Effect of DHA/EPA on sleep needs further investigation.

# Acknowledgements


- Professor Michael Crawford of Imperial College London – the “father” of DHA neuroscience
- Also to Captain Joe Hibbeln, Nicholas Bazan, Stephen Cunnane, Richard Bazinet and the many other scientists referenced in this presentation.
- And to my DSM colleagues: Norm Salem, Karin Yurko-Mauro and Sheila Gautier.

# Thank you