Regulatory & Labeling Challenges for Omega-3 Products

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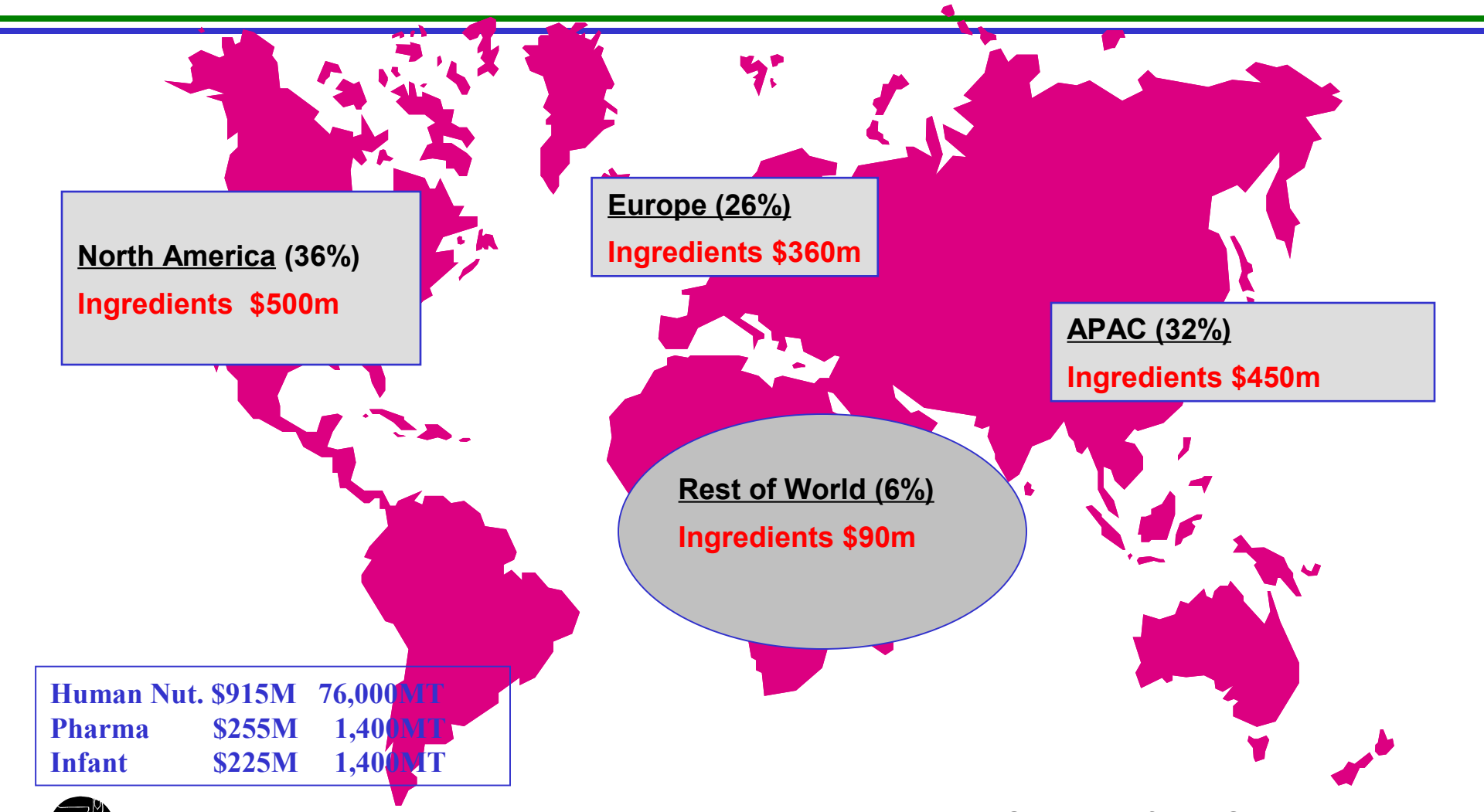
Milestones and Historical Perspective

- 1780: Fish oil (CLO) taken for arthritis relief
- 1935: Prostaglandins (PG) discovered
- 1970: Eicosanoid, leucotriene, prostaglandin metabolism elucidated
- 1971: Prostaglandins recognized as causing bad inflammatory health effects
- 1971: Dyerberg & Bang showed diet high in LC lipids reduced heart disease
- 1982: Nobel prize awarded for PG discovery and role in human health
- Late 1980's: Growing scientific data on benefits of LCP for CVD
- Late 1980's-early 1990's: supplements of LCP launched for CVD and general health
- 1985-1990: Benefits of LCP shown for the developing embryo and infants
- Early-Mid 1990's: Large ingredient companies enter fish oil business and specialty refining commences. Investments made in research and marketing
- Early 2000's: Explosion in science papers on LCP, NGO recommendations and governments permit fortification, some RDA's developed

LC Omega-3 Ingredient Revenue 2009

Global Ingredient Sales = $1,400M



Human Nut.	$915M	76,000MT
Pharma	$255M	1,400MT
Infant	$225M	1,400MT

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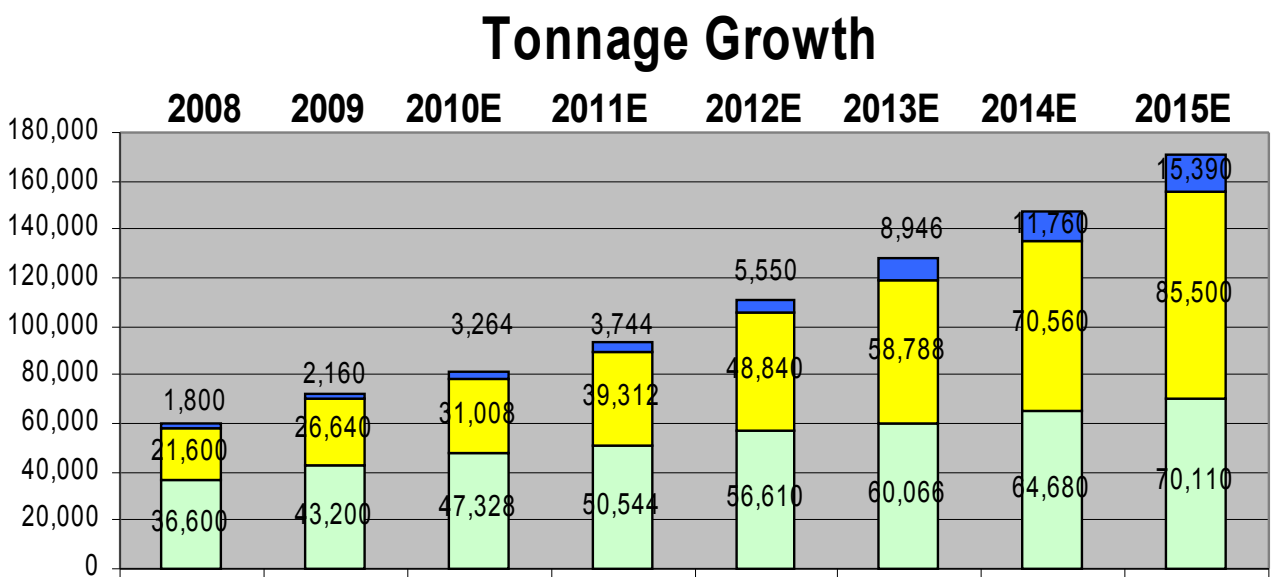
Worldwide Supply Refined Oils: ~80,000 MT

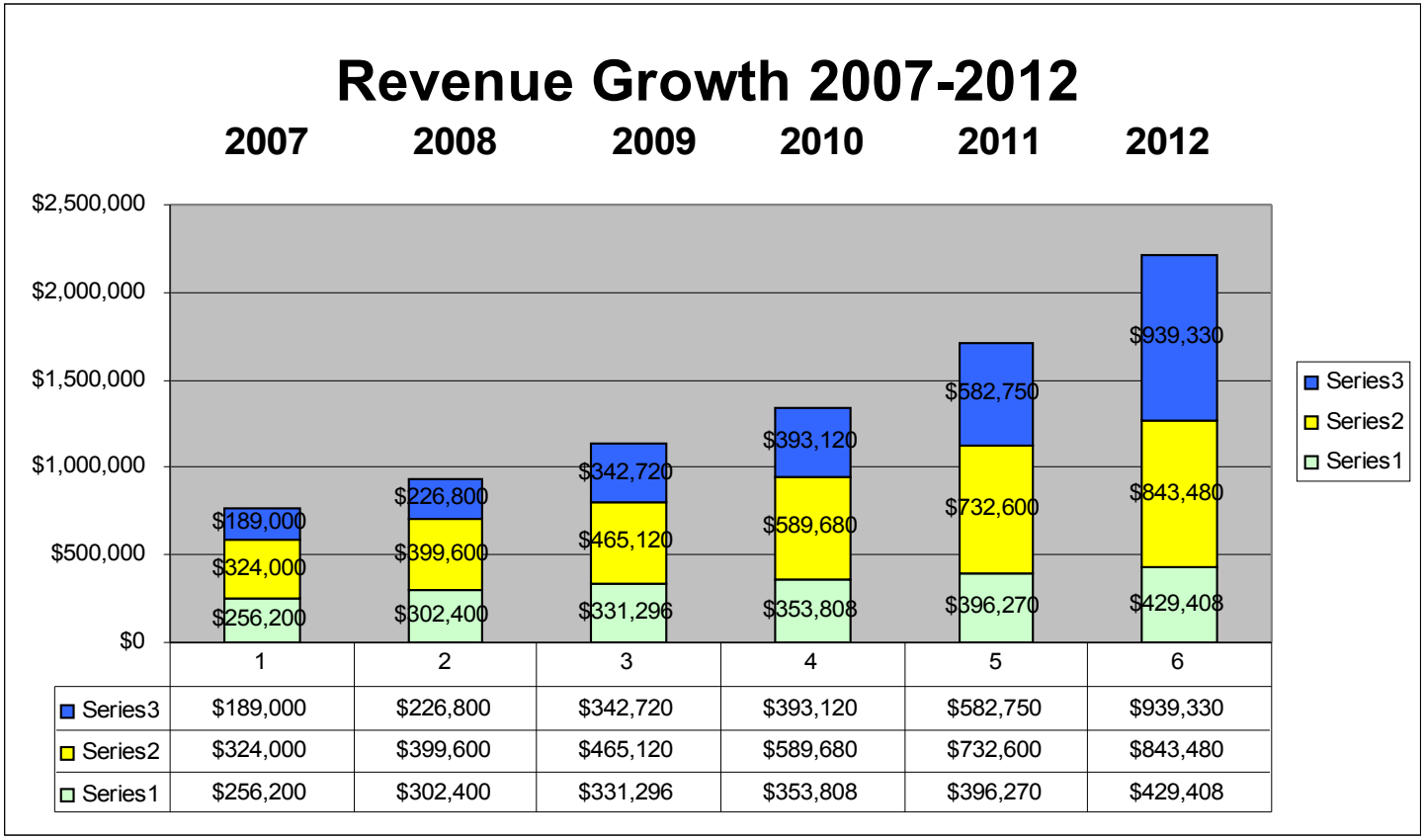
Growth of Omega-3 Oils 2008-2015

(tons refined oil, does not include Inf. or Pharma use)



	1	2	3	4	5	6	7	8
Powder expressed as 18/12 (oil as RM,30%ai)	1,800	2,160	3,264	3,744	5,550	8,946	11,760	15,390
50% Concentrates expressed as 18/12	21,600	26,640	31,008	39,312	48,840	58,788	70,560	85,500
18/12 Oils	36,600	43,200	47,328	50,544	56,610	60,066	64,680	70,110

Global Fish Oil Market
Ingredient Revenue Growth 2007-2012



	1	2	3	4	5	6
Series3	$189,000	$226,800	$342,720	$393,120	$582,750	$939,330
Series2	$324,000	$399,600	$465,120	$589,680	$732,600	$843,480
Series1	$256,200	$302,400	$331,296	$353,808	$396,270	$429,408

Powders

Concentrates

Oils

$769,200 **$928,800** **$1,139,100** **$1,336,600** **$1,711,600** **$2,212,200**

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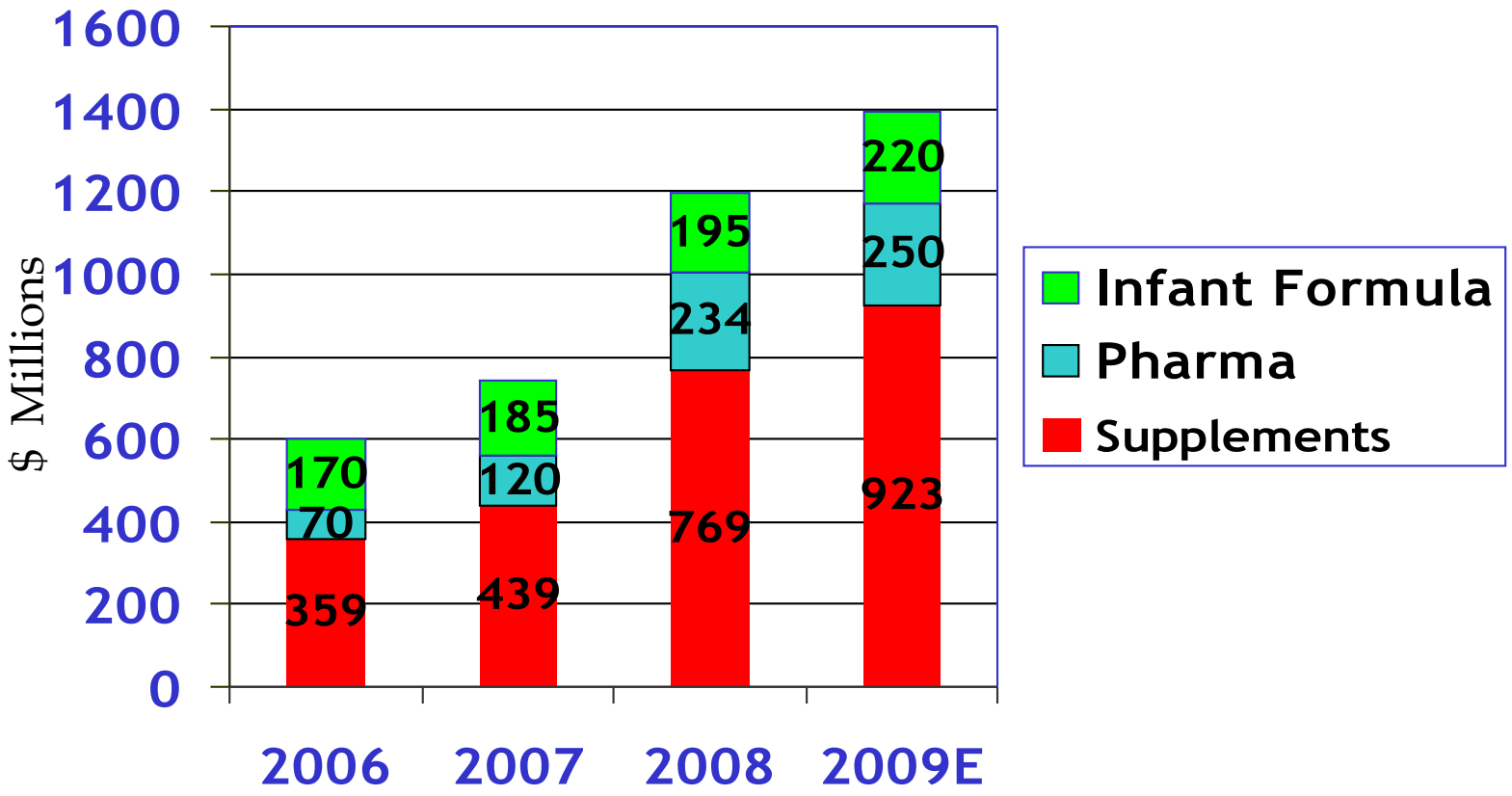
Global Sales Estimates of Bulk Omega-3 LCP Oils: Major Sectors 2006-2009 (Millions Dollars)



Key Issues Exist for Omega-3's

- Government recommendations (RDA's) not widespread
- Health Claims- few available, US and UK
- TG not recognized as major CVD factor
- Health professional support now building
- Quality of raw materials: safety, supply
- Consumer awareness/confusion (EPA,DHA, ALA, good fat)
- Plant oils vs. fish oils
- Many health benefits, confuses consumers
- Taste/stability (Raw Material and food forms)
- Food companies slow to fortify (cost, no RDI)
- Safety (unfounded)

Key Regulatory Issues for Omega-3's

- RDA's, RDI's
- Health Claims- few available, US and UK
- Government Recommendations/Guidelines
- Quality standards/monographs
- EU Hygiene Rules for foreign produced oils
- European Food Safety Agency (EFSA) Health Claims process/rules
- Infant formula ingredient requirements Indonesia
- Global standards for human use (CODEX)

Omega-3's: Large & Growing Science Base

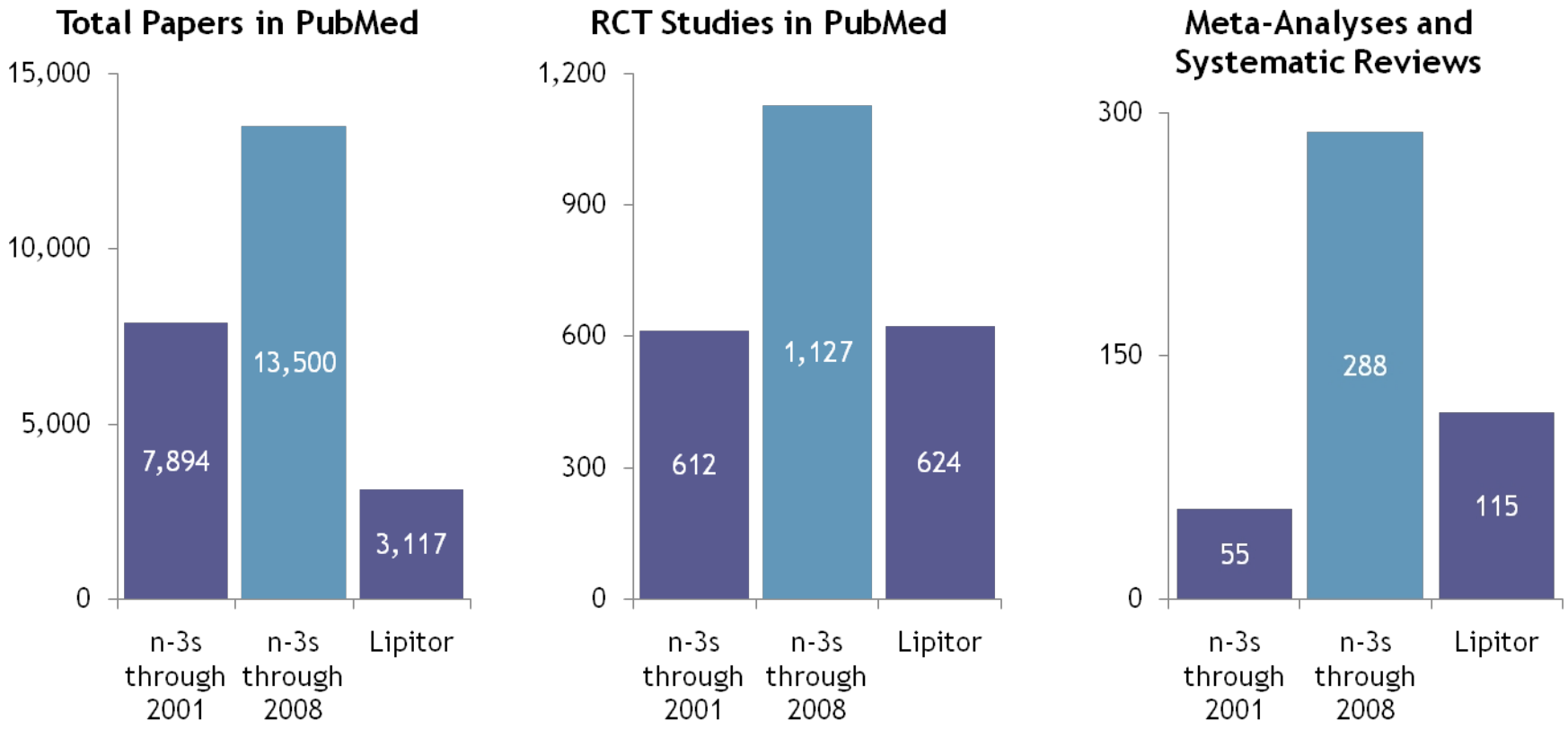
- >16,000 published papers
- Several critical meta analyses show health benefits, particularly CVD
- Excellent rationale based on the science and the human inflammatory response
- Brain and eye function with a well documented need for DHA and possibly EPA
- Other inflammatory based diseases
- IOM Reviews (2002,2005)
- AHRQ Reports 3/2004 confirm the science
- Very long history of use
- Gene signaling by omega-3's a new frontier for research

Clinical Conditions with Involvement of Omega-3 EPA/DHA

- **High blood pressure**
- **High Triglycerides**
- **Infant mental & visual development**
- **Secondary CVD**
- **Primary CVD**
- **Rheumatoid Arthritis**
- **Angina pectoris**

- Asthma
- Inflammatory diseases (e.g. GI tract)
- Eczema
- Degenerative neurologic disorders, dementia
- Depression
- Bipolar disorder
- Crohn's disease
- Bone health
- Macular degeneration

Published Papers on Omega-3 PUFA's



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Source: NIH Pubmed Database

EPA/DHA Support Healthy Cardiovascular Function

Paper	Implication
Mayo Clinic Proceedings (2008)	Asserts that the general population should aim for 500mg/day to reduce cardiovascular disease risk
American Dietetic Association (2007)	Asserts that AIs are low and that science supports that Americans should consume 500mg/day
Dietary Guidelines Advisory Committee Report (2005)	Recommends population consume two servings of fish per week, based on a 496mg/day intake recommendation
AHRQ Report on Omega-3s and Cardiovascular Disease (2004)	Reviewed evidence through 2004 and established that omega-3 consumption reduces CVD risk
GISSI Study (1999)	Established that EPA/DHA help prevent CVD-related deaths

USA Daily Value Process

1968 vitamin & mineral allowances

Periodic safety updates

RDIs

For vitamins & minerals

IOM Dietary Reference Intakes

Surgeon General Reports

Dietary Guidelines For Americans

DRVs

For nutrients important to health & nutrition

DVs

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RDI on the Way!? August 2009 Paper

Recommended Daily Dose for Omega-3 May Be on the Way New Analysis May Pave the Way for Greater Acceptance of Fish Oil Nutrient

By PEGGY PECK and DAN CHILDS
ABC News Medical Unit in Collaboration with MedPage Today

STATE-OF-THE-ART PAPER
Omega-3 Polyunsaturated Fatty Acids and Cardiovascular Diseases

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Manuscript received February 5, 2009; accepted February 25, 2009.

Am Coll Cardiol, 2009; 54:585-594, doi:10.1016/j.jacc.2009.02.084

Omega-3 LC-PUFA Science Base

Molecule	Target indication	Scientific evidence	Gov Rec's.
LC PUFA EPA	CVD-Heart health	Unequivocal	Yes
LC PUFA DHA	Infant/toddler brain/vision	Very strong	Yes
LC PUFA EPA	Enteral Nutrition	Excellent science	
LC PUFA DHA	Elderly Cognition	Considerable science	
LC PUFA DHA	Depression/mood suicide, child behaviour	Considerable science	
LC PUFA EPA	Joint health	Sound rationale, varied results	
LC PUFA DHA	Elderly, dementias ALZ	Science building	
LC PUFA EPA	Skin, allergy, GI	Emerging science	
LC PUFA EPA/DHA	Elderly AMD, diabetes Bone health	Emerging science	

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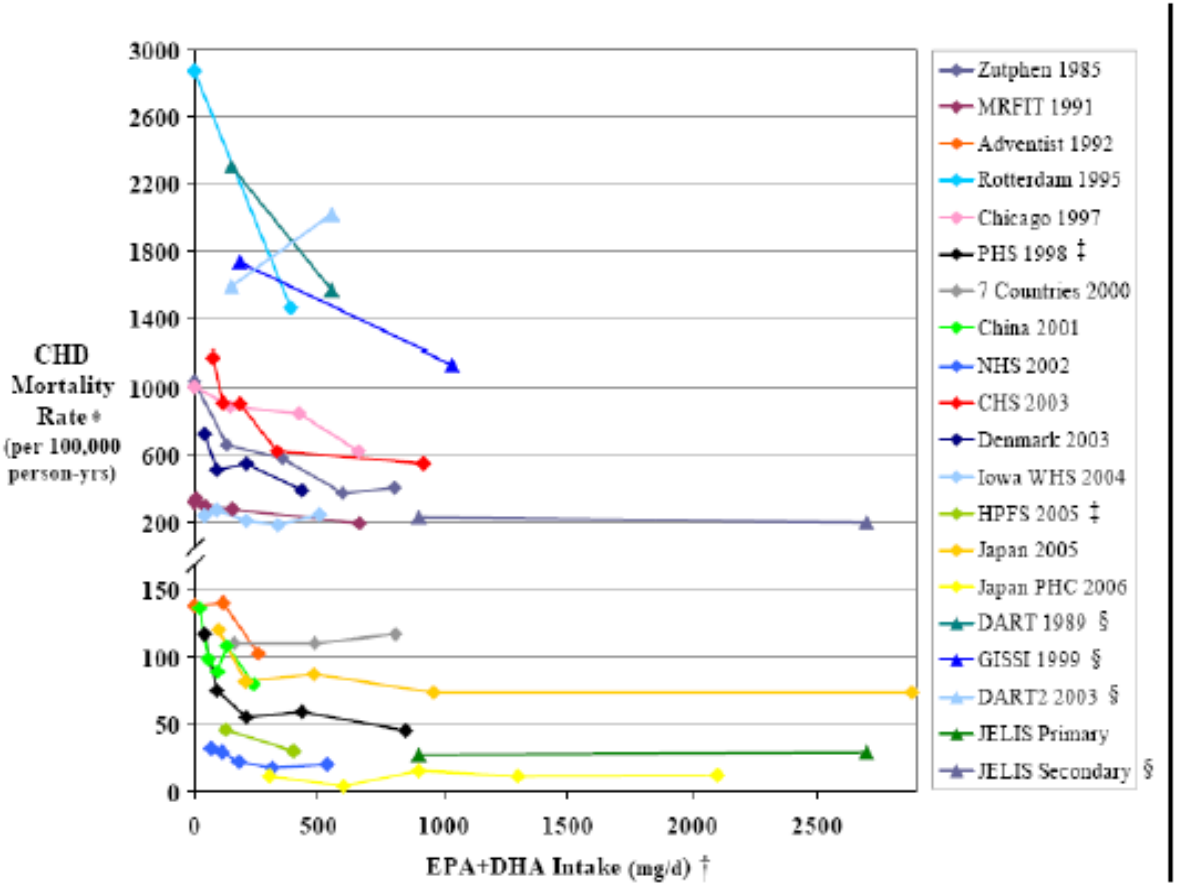
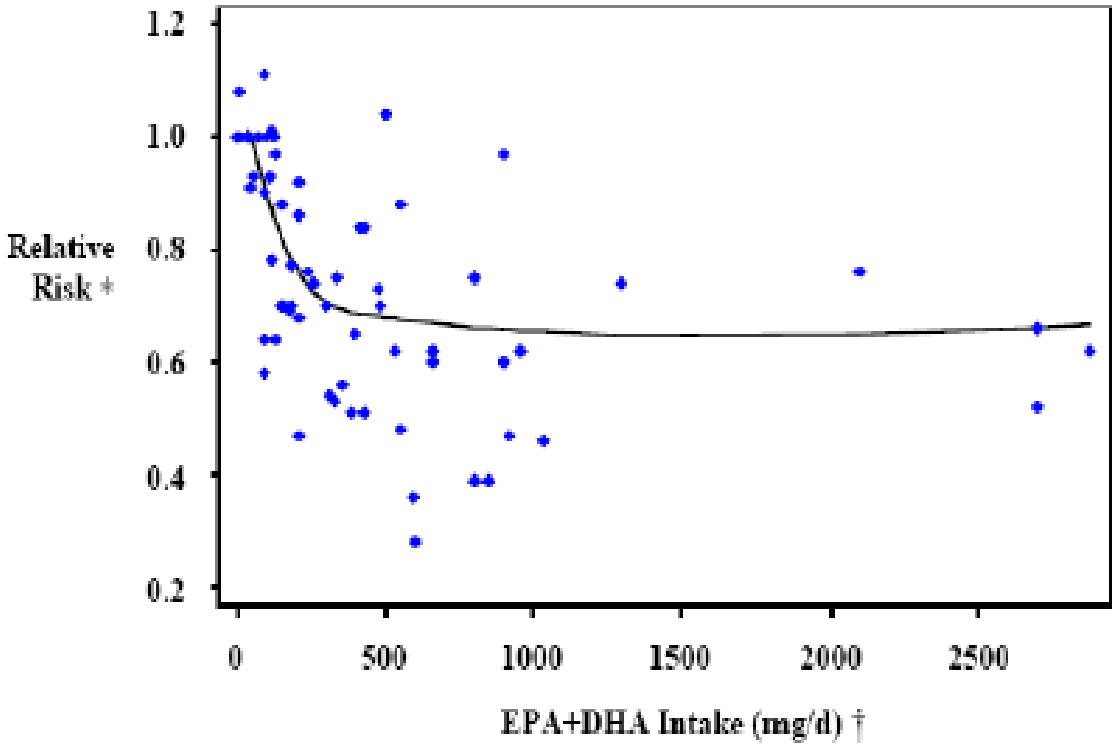
Government Guidelines, Regulation/Support

Figure D3.2a. Relationship between intake of fish or fish oil and relative risks of CHD death in prospective cohort studies and randomized clinical trials

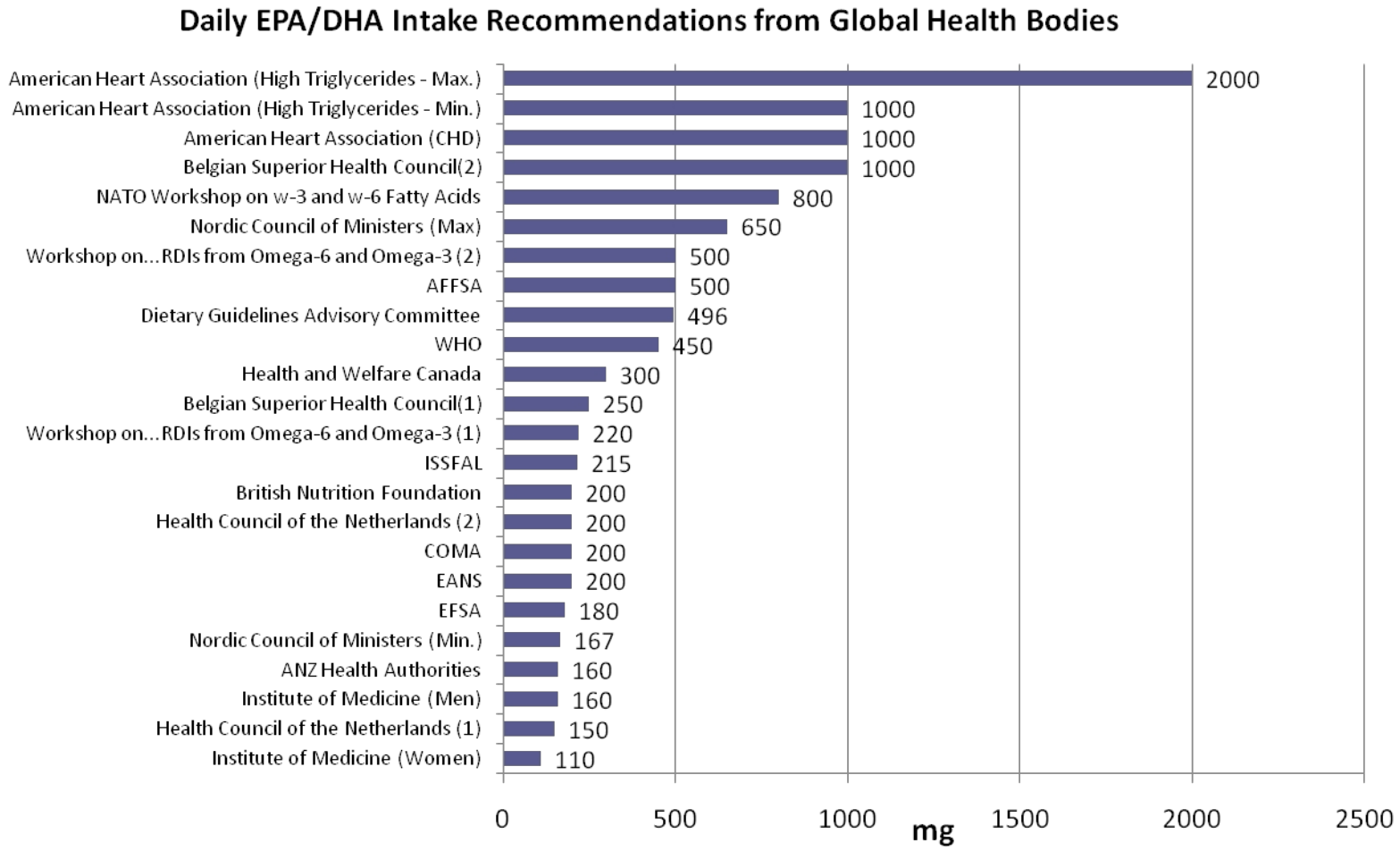


Government Guidelines, Regulation/Support

Figure D3.2b. Relative risk of coronary heart disease death by dose of EPA+DHA



Numerous health bodies have set intake recommendations



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Source: Various

Source: GOED

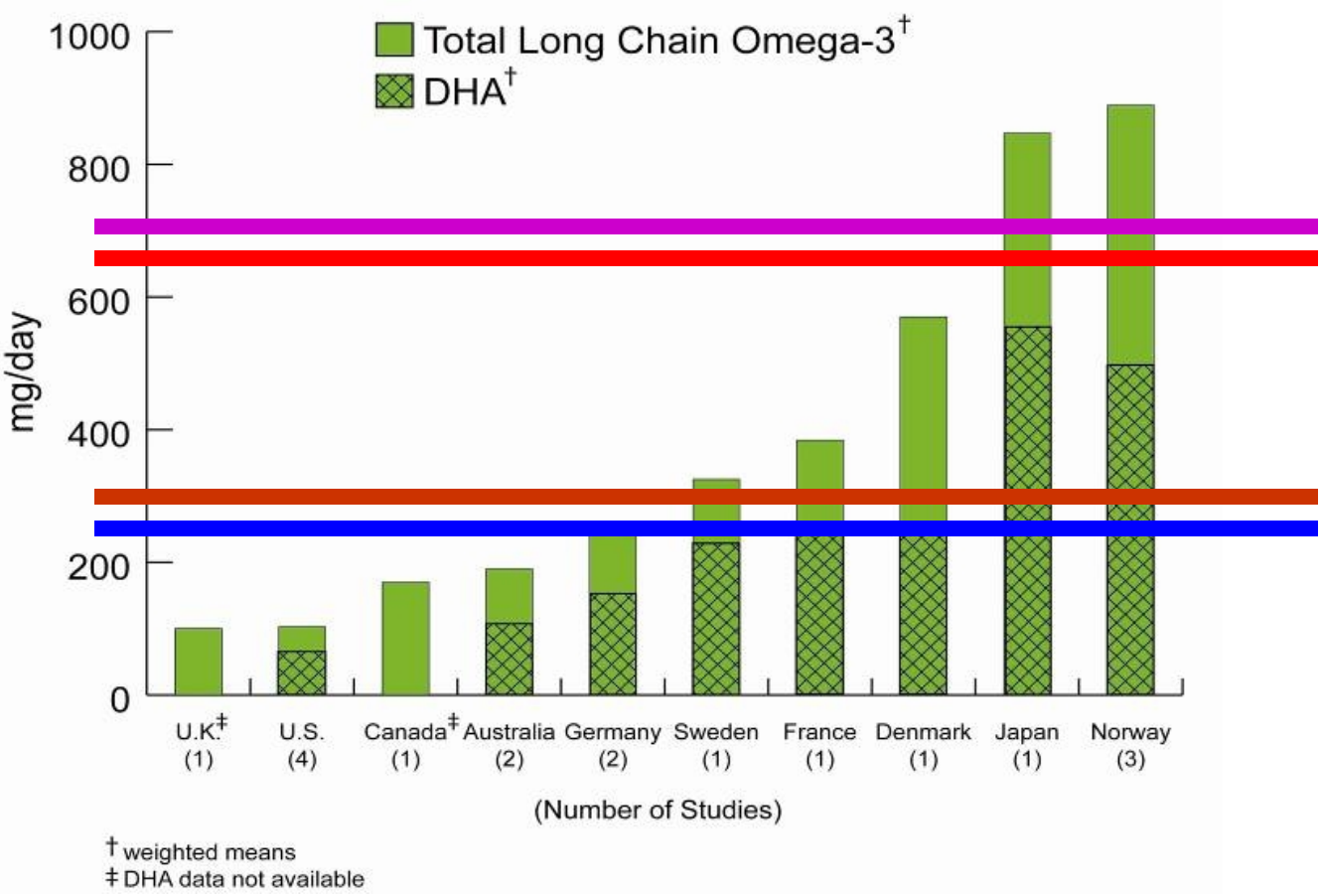
Current Global Adult Intakes versus Recommendations of Long-Chain Omega-3s

Recommendations:

LC n-3
ADA (2007)
ISSFAL (2004)
WHO/FAO (2003)
France (2001)
UK (2003)
Netherlands (2006)
Canada (2005)
Australia (2005)

DHA alone
France (2001)

Intake:



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Source: GOED

List of sources available upon request

The Science Supports RDI Establishment.

Additionally, prospective cohort studies and secondary prevention trials provide methodologically strong evidence that consumption of *n*-3 fatty acids from seafood and plant sources has a significant cardio-protective effect and decreases cardiovascular mortality (Mozaffarian, 2008; Mozaffarian and Rimm, 2006).

Conclusion

Moderate evidence shows that consumption of two servings of seafood per week (4 oz per serving), which provide an average of 250 mg per day of long-chain *n*-3 fatty acids, is associated with reduced cardiac mortality from CHD or sudden death in persons with and without CVD.

Omega-3 / DHA & EPA Recommendations

- Dietary Guidelines Report (2010)
- Institute of Medicine (IOM) - US (2002/2005)
- Dietary Guidelines for Americans (USDA Food Guide Pyramid) (2005)
- PeriLip Consensus Conference – EU (2005)
- American Heart Association (2002/2006/2007)
- Food Standards Agency - UK (2004)
- Child Health Foundation (2001)
- International Society for the Study of Fats and Lipids (ISSFAL) (1999)
- World Health Organization (1994/2003)
- British Nutrition Foundation (1992/2000)

FDA issued a qualified health claim for Omega-3 fatty acids (2004)

- "Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease."

IOM Macronutrient Report (2005)

- AI (calculated) for DHA and/or EPA 160 mg for good health
- AMDR advises consumption of 133-267 mg/day DHA (and/or EPA) to reduce risk of cardiovascular disease

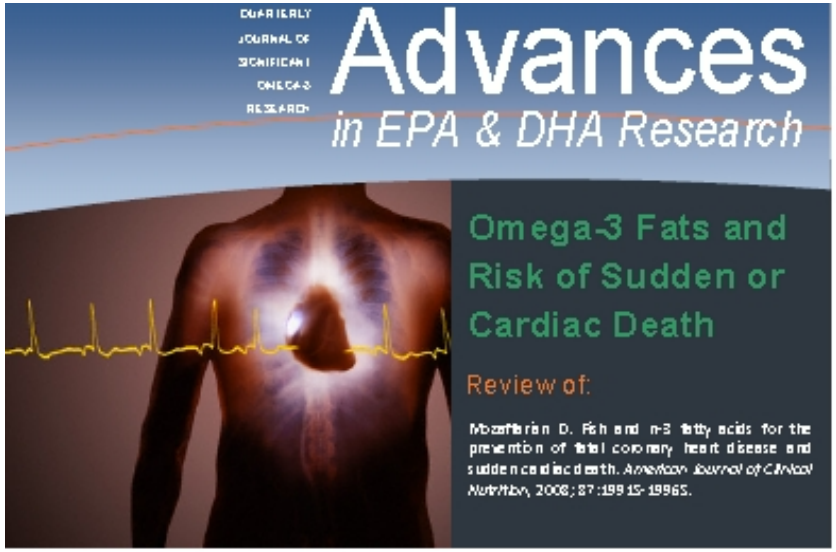
Place to Obtain Reputable Scientific Publications on Omega-3 EPA/DHA

Omega-3 Learning Center-Purdue University

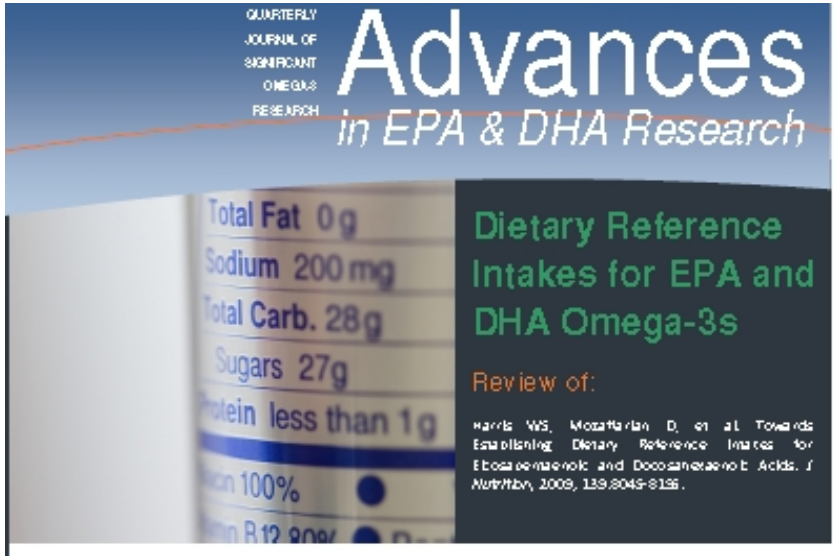
OMEGA-3 LEARNING for HEALTH & MEDICINE | Fact Sheet

National Institutes of Health (NIH)
National Library of Medicine Medline

Omega-3 Research Reviews- Cardiovascular Disease.



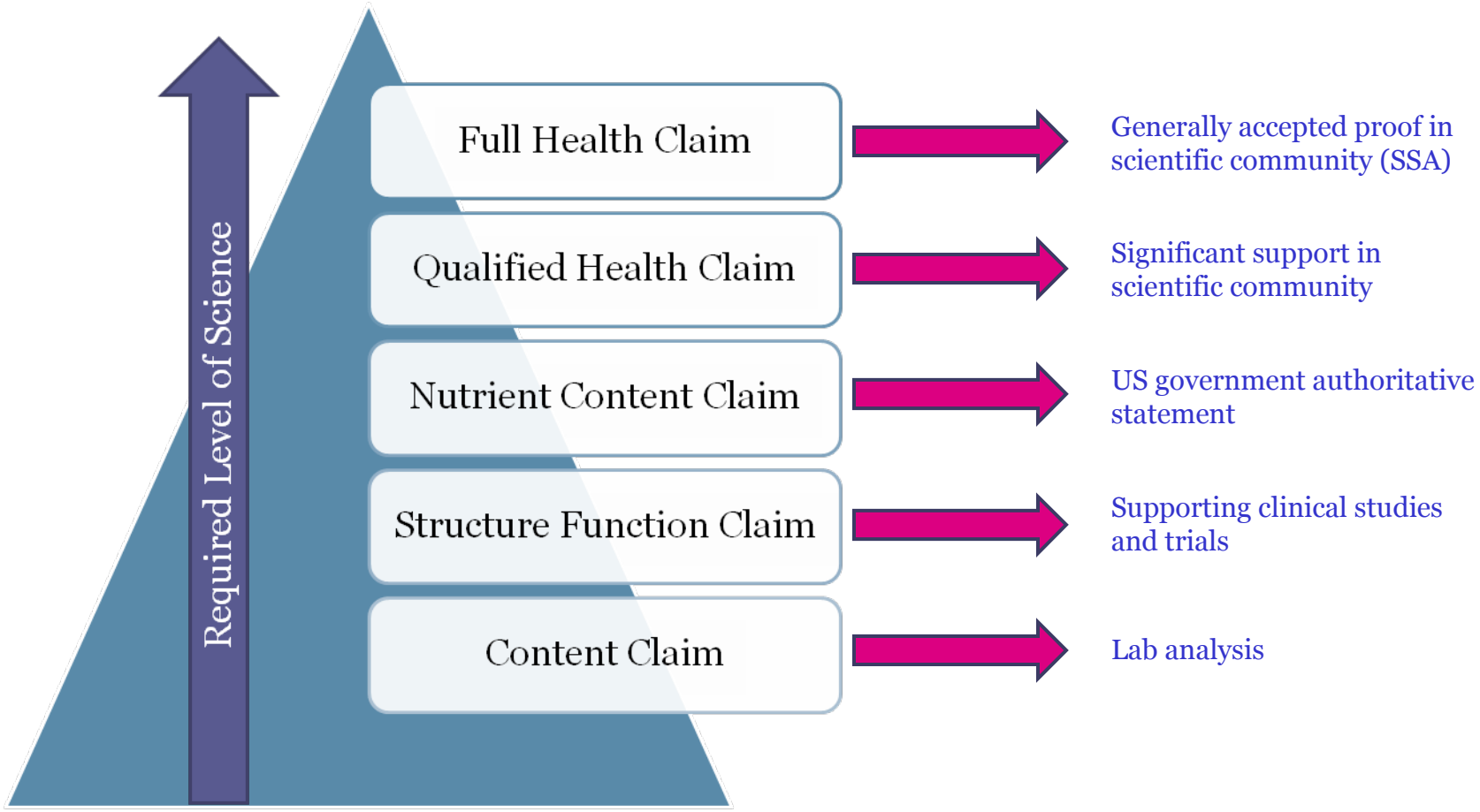
Consistent findings indicate a 36% reduction in risk of sudden cardiac death from modest consumption of EPA/DHA (250-500mgm/day).
Mozaffarian D. AJCN 2008.



There is a strong and compelling argument for establishing a 250-500 mg/day RDI for EPA/DHA.
Harris W. et al, J Nutrition 2009

Current US Claims for EPA/DHA Omega-3 fatty Acids

The level of science behind each claim is different



There are currently four types of claims available in USA for Long Chain Omega-3's

Claim Types	Examples
Full Health Claim	Not Available
Qualified Health Claim	"*Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease. One serving of [name of food] provides [x] grams of EPA and DHA omega-3 fatty acids. [See nutrition information for total fat, saturated fat and cholesterol content.]*
Nutrient Content Claim	*"Excellent Source of EPA & DHA Omega-3s"* *"Rich in EPA & DHA Omega-3s"*
Structure Function Claim	*"Supports a Healthy Heart"*
Content Claims	*"Contains 30mg of EPA & DHA Omega-3s"*

DHA & EPA Support Cardiovascular Health in Children and Adults

- Favorable effects on blood lipid profile
  - Reduced triglycerides (fasting and following a meal)
  - Increased HDL (good cholesterol)
  - Improved LDL particle size
- Modest reductions in blood pressure (higher doses)
  - Improved arterial compliance
  - Anti-thrombotic effects
- Cardiac rhythm
  - Stabilizes heart rhythm
  - Lowers heart rate

FDA Qualified Health Claim

Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease. One serving of (name of food) provides (x) grams of EPA and DHA omega-3 fatty acids."

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Normal Adult Cognitive Function

- Strong data from a US cohort (n=3718) supports a relationship between decreased cognitive decline and fish intake
  - 10% slower decline among subjects reporting 1 fish meal per week (about 80 mg); 13% slower with 2 fish meals per week

Morris et al. Arch Neruol, 2005, 62:1-5.

- Data from EU cohorts suggest a relationship between DHA and cognitive function
  - Whalley and coworkers studied 364 non-demented elderly from a cohort of 2000 studied for childhood IQ
  - Plasma DHA significant predictor of IQ at age 64

Kalmijn et al. Neurology, 2004, 62:275-80.
Whalley et al. AJCN, 2004, 80:1650-7.

The FDA is proposing to disallow nutrient content claims on EPA and DHA products

- FDA feels it can act on the claims now through rulemaking, rather than an assessment of notifications filed to date
- FDA believes no authoritative statement has been made establishing an intake level for omega-3s, thus there is no basis to make a nutrient content claim

FDA states specific requirements for an authoritative statement to be accepted

- Must come from a recognized scientific body of the US government
- Must set a nutrient level on which nutrient content claims can be based
- Accepted nutrient levels include; Recommended Daily Allowances (RDAs), Estimated Safe Intakes (ESIs) and Adequate Intakes (AIs)
- An AI is the average daily intake by generally healthy people that is assumed to be adequate

Quality & Safety GOED Omega-3 Monograph

TESTS

Acid value.	Maximum 3 mg KOH/g; AOCS Official Method Cd 3d-63
Peroxide value.	Maximum 5 meq/kg; AOCS Official Method Cd 8-53
Anisidine value.	Maximum 20; AOCS Official Method Cd 18-90
TOTOX.	Maximum 26 (result of calculation, (2 x PV) + AV)
PCDDs and PCDFs.	Maximum 2 pg WHO-PCDD/F-TEQ/g
PCBs.	Total PCBs should be expressed on a weight/weight basis and should include IUPAC congeners 28, 52, 101, 118, 138, 153 and 180 Maximum: 0.09 mg/kg
Dioxin- like PCBs	Maximum 3 pg WHO -TEQ/g (maximum for Dioxin and Furans remains at 2pg/g).

Heavy Metals.

Lead (Pb):	Less than 0.1 mg/kg
Cadmium (Cd):	Less than 0.1 mg/kg
Mercury (Hg):	Less than 0.1 mg/kg
In-organic Arsenic (As):	Less than 0.1 mg/kg

Only GOED Members sign affidavits that their product meets or exceeds the Monograph.

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EU Food Hygiene Regulations

- Proposed EU food hygiene rules would have created problems for fish oil imports to EU
- GOED working with regulators now have fish processors approved, utilizing agreed processing times and rancidity levels. Generally all boats and fleet licensed
- Tuna oil from Taiwan going to Japan OK since refining in Japan meets regs.
- Majority of oil is from Chile and Peru

EFSA Health Claims

- Several well documented Article 14 claims (Health Claims) for LCP sent to Panel for ruling: claims for vision and brain development are or will likely be approved
- Many submissions by organizations rejected due to incomplete dossiers
- Like many other nutrient submissions the standards for allowing claims set VERY high and similar to drug requirements, requiring multiple DBPCT trials.
- Many nutrient claims to date have been rejected on this basis and there is considerable discussion as to whether those organizations should continue to fight for claims. Some companies have withdrawn submissions
- EFSA LCP Article 13.1 claims (s/f claims) two approved, dosages of N-3 issued BUT no specification for a level in products.

for maintaining normal TG levels; maintenance of normal BP.

Infant Formula Issues

- Indonesian Infant Formula Ingredient Review
  - Initially only LCP's permitted algal oils
  - Following academic and corporate submissions algal, fungal and fish oil now possible IF they meet stringent standards
  - The proposed standards are derived from a variety of documents and require discussion with authorities
  - Changes now made but the standards higher than previously
- CODEX Standards for fish oils in human use.
  - Submission from Swiss delegation
  - Not all countries delegates are supporting
  - Monograph will be developed at some point
  - CODEX moves exceedingly slow

Key Issues/Success Drivers for Omega-3's

- Government recommendations (US RDI)
- Health Claims- few available, US and EFSA
- TG not recognized as major CVD factor
- Health professional support
- Consumer awareness/confusion (EPA, and ALA, good fats, plant oils vs fish oils)
- Too many health benefits, confuses consumers
- Quality of raw materials: safety, supply
- Taste/stability (RM and food forms)
- Food companies slow to fortify

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