

Nutrition and Health
Series Editor: Adrienne Bendich

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Ronald Ross Watson
Sherma Zibadi *Editors*

Omega-6/3 Fatty Acids

Functions, Sustainability Strategies
and Perspectives

 Humana Press

NUTRITION AND HEALTH

Adrienne Bendich, PhD, FACN, SERIES EDITOR

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OMEGA-6/3 FATTY ACIDS

Functions, Sustainability Strategies and Perspectives

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Series Editor Page

The great success of the Nutrition and Health Series is the result of the consistent overriding mission of providing health professionals with texts that are essential because each includes: (1) a synthesis of the state of the science, (2) timely, in-depth reviews by the leading researchers in their respective fields, (3) extensive, up-to-date fully annotated reference lists, (4) a detailed index, (5) relevant tables and figures, (6) identification of paradigm shifts and the consequences, (7) virtually no overlap of information between chapters, but targeted, inter-chapter referrals, (8) suggestions of areas for future research and (9) balanced, data-driven answers to patient as well as health professionals questions which are based upon the totality of evidence rather than the findings of any single study.

The series volumes are not the outcome of a symposium. Rather, each editor has the potential to examine a chosen area with a broad perspective, both in subject matter as well as in the choice of chapter authors. The editor(s), whose training(s) is (are) both research and practice oriented, has the opportunity to develop a primary objective for his or her book, define the scope and focus, and then invite the leading authorities to be part of his or her initiative. The authors are encouraged to provide an overview of the field, discuss their own research and relate the research findings to potential human health consequences. Because each book is developed *de novo*, the chapters are coordinated so that the resulting volume imparts greater knowledge than the sum of the information contained in the individual chapters.

“Omega-6/3 Fatty Acids: Functions, Sustainability, Strategies and Perspectives,” edited by Fabien De Meester, PhD; Ronald Ross Watson, PhD; and Sherma Zibadi, is a welcome addition to the Nutrition and Health Series. Long-chain fatty acids are critical for the formation of membranes within each cell of the body and are uniquely involved in neurological and cardiovascular functions. Over the past decade, there has been an increased interest in the importance of consuming diets containing higher-than-average intakes of the longest chain omega-3 fatty acid, docosahexaenoic acid (DHA), as survey data consistently point to reductions in risks of many chronic diseases in the populations with the highest intakes. A critical issue involves the sustainability of natural sources of DHA as deep-sea cold-water fish are not a limitless source. However, other sources are being developed as are novel production methodologies. Thus, it is timely to examine the current intakes of populations around the world, review the key findings of benefits from higher-than-average intakes of DHA and other long-chain omega-3 polyunsaturated fatty acids (PUFA) and discuss the strategies currently available to enhance the sustainability of sources of these biologically important oils. Both quality and regulatory issues are considered in depth in separate chapters. Also, there are discussions of the potential health savings that could be accrued by consuming a more health-enhancing

ratio of omega-3 to omega-6 long-chain PUFA. This volume combines the latest molecular and clinical science with critical information about sources of omega-3 fatty acids and the protective processes involved in bringing these otherwise highly oxidizable oils to the marketplace and into consumers' homes. The editors have developed a unique volume that contains both theoretical as well as pragmatic chapters that help the reader to better understand the importance of balancing the fats we consume in order to obtain the documented health benefits.

The 22 chapters examine the biological as well as clinical consequences of long-chain omega-3 deficiency and review the data related to status throughout the lifespan and the beneficial effects of optimal omega-3 to omega-6 ratios. The book is logically organized in four sections and begins with an overview section that includes three informative chapters including an historical perspective on the biological functions of long-chain fatty acids. The second chapter, authored by Dr. William Lands, a leading authority on the value of fish in the diet and the importance of balancing dietary intakes of omega-3 and omega-6 fatty acids, reminds us of the health consequences of consuming too much omega-6 and insufficient omega-3 over a prolonged period of time. The figures included in this chapter help to visualize these important dietary balances. The third chapter reviews the up-to-date information regarding the effects of omega-3 at the cellular level and their effects on gene expression. This chapter describes in detail the different genes and genetic activities that are affected by omega-3 status and includes information on the role of these oils in determining telomere lengths. Availability of long-chain PUFAs during human evolution is reviewed and related to the Columbus Concept. The value of higher omega-3 levels in certain tissues and optimal functioning of these tissues is discussed. Omega-3 fatty acids are at high concentrations in the brain and can influence mind-body interactions that are known to modulate noncommunicable diseases, as described in the Tsim Tsoom Concept. The importance of the balance between omega-3 and omega-6 ingestion and the potential for disease prevention is critically reviewed in the third chapter that also makes clear recommendations on potential changes in diet to assure a more balanced intake of the fatty acids.

The second section on omega-3 status and functions begins with an overview of the methods used in assessment of omega-3 and omega-6 status, dietary sources of DHA and other omega-3-containing oils, and reviews the usefulness of developing omega-3 indexes to compare diets throughout life and when chronic diseases are present. Essential functions of long-chain PUFA in inflammation, endothelial function and cytokine regulation are discussed as well. Clinically relevant data on the role of PUFA in cardiovascular disease as well as placental and neonatal neurological functions are examined in depth. The following chapter examines the many factors that affect omega-3 status and tabulates data on norms for infants, young children and adolescents and adults. In addition to age and sex, dietary factors and health status also affect the level of circulating long-chain polyunsaturated fatty acids (PUFA). A unique chapter reviews the requirements for DHA during the second half of infancy when many children begin consuming more than breast milk or other milk sources. During this time of overall rapid growth as well as rapid brain growth, the need for dietary sources of DHA may be reduced compared to the first 6 months of life. This deficit may be associated with measurable reductions in visual acuity as discussed in this informative chapter.

Two of the major organs that concentrate omega-3 fatty acids are the brain and the retina. The next chapter documents that the eye and brain also use a majority of the energy generated by the entire body. Of interest, 93% of the omega-3 fatty acids in the retina are DHA. The human brain's gray matter is enriched with arachidonic acid (AA), a long-chain omega-6 fatty acid, and DHA, which together account for 20% of the brain's membrane fatty acids. This unique chapter describes the latest research linking omega-3:omega-6 ratios to dry eye syndrome and age related macular degeneration. The long-chain PUFAs, DHA and AA are essential for normal brain development and function. Since DHA and AA synthesis from shorter-chain precursor essential fatty acids by fetuses and neonates is often limited, both long-chain fatty acids are delivered by maternal blood to the placenta and breast milk, and are currently supplemented in the majority of breast milk substitutes.

Western diets are often poor in long-chain omega-3 PUFAs and this is often reflected in comparatively low DHA and eicosapentanoic acid (EPA) blood levels in pregnant or lactating women. Several observational studies have shown that infants from mothers with a higher DHA status performed significantly better on cognitive tests. However, as not all studies have shown benefits, this chapter reviews the totality of the data to provide an objective view of the current state of the science. The chapter's excellent tables, figures and over 150 references are of great value to the clinician or other health professional who provides balanced advice to clients and/or patients. Long-chain omega-3 PUFA have also been examined as possible adjuncts in psychotic diseases and also for reduction of risk for individuals with serious psychiatric disorders. The chapter reviews the epidemiological inverse associations between low omega-3 intakes and increased risk of schizophrenia, the potential for omega-3 supplementation to reduce both certain adverse effects associated with anti-psychotic drugs and dosage of certain drugs. This highly referenced chapter provides comprehensive tables that review relevant clinical studies.

The mechanisms by which omega-3 fatty acids can affect cardiovascular and brain functions are described in detail in the next chapter. The evidence that a pathological dysfunction of the endocannabinoid system might affect the development and progression of psychotic diseases as well as cardiovascular diseases is reviewed. Emphasis is placed on discussions of endogenous cannabinoids, called endocannabinoids. These hormone-like molecules can affect intracellular gene expression in peripheral tissues and alter responses in heart, blood vessels and the central nervous system. The ratio of omega-3 to omega-6 in blood may result in variable levels of endocannabinoids. The chapter additionally describes the relevance of krill oil as a source of omega-3 fatty acids versus fish oils. The final chapter in this section describes the importance of DHA in the process of angiogenesis. The emphasis is placed on the development of the placenta where DHA enhances blood vessel development that is critical for the growth of the fetus. In contrast, in cancer, angiogenesis enhances tumor growth and recent laboratory animal studies indicate that DHA reduces angiogenesis in models of carcinogenesis.

In addition to the brain and retina, the testes and sperm also contain high concentrations of DHA. Evidence suggests that dietary intake and circulating levels of DHA can directly influence sperm DHA as well as the sperm's DNA and sperm motility by regulating smooth muscle contractility and excitability and oxidative stress. Free radical

damage from oxidative stress can result in germ line mutations and these would increase with age. Associations between inherited neurological conditions such as autism, older fathers, and low DHA status are reviewed as is the importance of DHA in mitochondrial membrane stability.

The third section contains unique chapters that expand upon the earlier chapters that indicate that there is a consistent lower-than-optimal intake of omega-3 fatty acids around the globe. There are few natural sources of long-chain omega-3 fatty acids and the ability of humans to elongate shorter-chain fatty acids is limited. There is also the critical issue of sustainable sources of long-chain PUFA especially for use in pharmaceutical drugs, dietary supplements, and as additions to foods. Thus, a number of strategies are explored by chapter authors that could help assure adequate supplies for the growing world population. There is agreement that currently there is no shortage; however deep-sea cold-water fishing, the current major source of long-chain omega-3 fatty acids, is being curtailed to assure that species survive.

As mentioned above, marine crustaceans, known as krill, are being used as a new source of DHA and the comprehensive and thoughtful chapter that describes this potential source also examines the potential effects on Antarctic and other ecosystems of large-scale harvesting of a natural resource. Discussions between national and international working groups are provided. An important example cited by many chapter authors is the recommendations of the Global Summit on Nutrition, Health and Human Behaviour of a target intake of long-chain omega-3 of about 1 g day and therefore a need to “increase the availability of LC ω (omega)-3 (especially DHA) for human consumption in a sustainable, environmentally responsible way.”

The chapter on aquaculture provides an update on strategies to increase production of fish that are excellent sources of omega-3 fatty acids. A number of primary strategies, including novel sources of long-chain PUFA, modified lipids, and high PUFA sources near the time of harvesting have been proposed as means to maintain or increase levels of PUFA within farmed seafood. In addition to krill, there are a number of other new sources of long-chain omega-3 PUFA that also deliver the fatty acids in the form of phospholipids rather than the standard triglyceride or ethyl ester forms currently in the majority of fish oil capsules. The next chapter describes the potential for using fish eggs and fish meal as sources of marine phospholipids and describes the benefits of these sources. Further clinical studies are needed to assure comparable efficacy with the already clinically tested oils.

Alpha-linolenic acid (ALA) is considered an essential fatty acid (EFA) since it cannot be synthesized by the body and therefore must be supplied by dietary sources. ALA is considered as a short-chain omega-3 fatty acid and can be converted to the longer chain DHA or EPA within the human body. ALA is therefore considered the building block of long-chain omega-3 PUFA and its dietary sources include nuts, seeds and certain edible plants. This chapter examines the plusses and minuses involved in utilizing these sources of ALA to fulfill the requirements for long-chain PUFA.

The final section of this comprehensive volume examines the newest methods to enhance the availability of the long-chain PUFAS from fish, krill, and newer sources discussed above. The final two chapters examine the importance of quality control to assure the biological value of these oils and the regulatory environment that protects the

consumer by assuring a set of standards for the development of product claims and quality. The industrial processing of fish and their oils is undergoing a transformation that is described in the next chapter. The use of lipases in edible oil processing is a relatively recent development compared to their more general use within food processing. Thus, there are methodologies currently available to produce a more concentrated source of long-chain omega-3 products for human use. The next chapter discusses the most common concentration technologies applied to obtain omega-3 concentrates well beyond the current levels of 18% EPA and 12% DHA. Special emphasis is given to two important techniques: supercritical fluid technology which includes both supercritical fluid extraction, and supercritical fluid chromatography and molecular distillation.

As important as sources of omega-3 fatty acid is the quality control processes that assure that products actually do contain what is on the label. The next chapter documents the importance of quality assurance programs and outlines the most reliable methods to measure fatty acids in oils. The chapter reviews in detail the methods that include gas chromatography, infrared spectroscopy, Fourier transform infrared spectroscopy and other methods of quantitative analysis and provides over 20 tables and figures to assist the reader in understanding these methods. Equally important are the regulations that control the quality and health claims permitted in the marketing of long-chain omega-3 fatty acids. The final chapter reviews the regulatory environment and concentrates on the regulations from the European Food Safety Authority (EFSA) as this was the first international government agency to examine the health as well as disease prevention claims, safety and quality issues regarding these oils. The tables in this chapter outline all of the acceptable claims and the critical references are included.

The logical sequence of the sections as well as the chapters within each section enhance the understanding of the latest information on the current standards of practice for clinicians, related health professionals including the dietician, nurse, pharmacist, physical therapist, behaviorist, psychologist, and others involved in the team effort to assure optimal omega-3 intakes by their colleagues, clients, and/or patients. This comprehensive volume also has great value for academicians involved in the education of graduate students and postdoctoral fellows, medical students and allied health professionals who plan to interact with patients with disorders that may be beneficially affected by the addition of long-chain omega-3 containing products to the diet.

The volume contains over 125 detailed tables and figures that assist the reader in comprehending the complexities of the metabolism as well as the biological significance of long-chain omega-3 fatty acids for human health. The overriding goal of this volume is to provide the health professional with balanced documentation and awareness of the newest research and therapeutic approaches including an appreciation of the complexity of this relatively new field of investigation. Hallmarks of the 22 chapters include key words and bulleted key points at the beginning of each chapter, complete definitions of terms with the abbreviations fully defined for the reader, and consistent use of terms between chapters. There are over 1,300 up-to-date references; all chapters include a conclusion to highlight major findings. The volume also contains a highly annotated index.

This unique text provides practical, data-driven resources based upon the totality of the evidence to help the reader understand the basics, treatments and preventive and sustainability strategies that are involved in understanding of the role long-chain

omega-3 PUFA may play in healthy individuals as well as those with cardiovascular disease, diabetes, or neurocognitive declines. Of equal importance, critical issues that involve patient concerns, such as natural sources of long-chain oils and unique data on assessment of the oils as well as status, quality assurance and regulatory issues are included in well-referenced, informative chapters. The overarching goal of the editors is to provide fully referenced information to health professionals so they may have a balanced perspective on the value of various preventive and treatment options that are available today as well as in the foreseeable future.

In conclusion, “Omega-6/3 Fatty Acids: Functions, Sustainability, Strategies, and Perspectives,” edited by Fabien De Meester, PhD, Ronald Ross Watson PhD, and Sherma Zibadi, MD, PhD provides health professionals in many areas of research and practice with the most up-to-date, well-referenced, and comprehensive volume on the current state of the science and medical uses of long-chain omega-3 fatty acids. This volume will serve the reader as the most authoritative resource in the field to date and is a very welcome addition to the Nutrition and Health Series.

Adrienne Bendich, PhD, FACN, FASN

Preface

Over the past several years we have noted a substantial increase in the amount and novelty of research involving omega fatty acids in health promotion and disease prevention. Therefore we felt it was appropriate to bring together experts involved in the research and its analysis with the focus on human health improvements and actions that should now be taken. Our goals included:

- *First* brain and heart disorders resulting from long-chain omega-3 (EPA+DHA) deficiency. They are one of the biggest challenges to the future human health. Such health costs are devastating health care and threatening economic instability.
- *Second* assessment of status is critical for public health. Thus professional need to modulate the relative tissue concentration of long-chain omega 3 to long-chain omega 6, in the population over a lifetime, a daunting challenge. Assessment of tissue status in an easy and economic method is needed.
- *Third*, for the many people consuming Western-type diet reaching a balance of omega 3 and omega 6 fatty acids in tissues fall far short of basic needs for health. Thus how to improve intake including via supplementation is a focus of the book and should be for health professionals.

On the Science behind the economics of the omega-6/3 fatty acids, William Lands states “we must not think that thunders cause rain” in an attempt to help rescue health care professionals addressing symptoms rather than causes of diseases. The potential saving is enormous and so is the current disaster in terms of spending. The change is at anyone’s reach. Lands’ chapter is conducive to the launch of his new “gadget” developed with the purpose in mind to help anyone reaching out with long-term health, i.e., prevention of diseases. Quoting him on the launch: “Finally, we have an ‘app’ to help you learn and teach others about the balance of Omega-3 and Omega-6 nutrients in the foods that you eat.” Clemens von Schacky reviews medical progress to date with the highly standardized Omega-3 Index and identifies a possible 8–11% ideal target range for future ill-health prevention at large and for immediate application in preventive cardiology, pregnancy and lactation, and depression. Claudio Galli emphasizes the very individual nature of the fatty acid status in humans with variables extending from age to physiological (mind ↔ body) conditions to lifestyle including diet/matrix, to geographical situation including circadian rhythm (chronobiology). Ram Bahadur Singh et al. look at the molecular relevance of omega-3 fatty acids in genetic expression (nutrigenetics); noncommunicable diseases are multifactorial and polygenic in nature—feeding genes the evolutionary dietary ratio of essential fatty acids (omega-6/3~1) may well be the determinant factor in silencing polymorphisms and phenotype expression on noncommunicable diseases. Jeffrey Anshel’s introduction, “the eye is not simply a window

to the soul, but actually is a mirror of the body” reflects on the essentiality as well as the urgency, to consider mind ↔ body approaches to preventing noncommunicable diseases including dry eyes and age-related macular degeneration. DHA—the information receptor—and EPA—the anti-inflammatory eicosanoid fatty acid—obviously are center to the theme here. Jan-Philipp Schuchardt and Andreas Hahn report in detail on the accumulating literature testing for a potential relationship between cognitive and mental development and dietary omega-6/3 fatty acids in pregnant and lactating mothers as well as in newborns and young infants. No wonder that current evidence no matter how encouraging suffers from the current inability of Western medicine to approach inception and development from a more holistic mind ↔ body angle, leaving mind-related confounding factors in the darkness. Nilufar Mossaheb et al. entertain us on psychotic disorders and the plausible disease-fatty acid (EPA and DHA) structure/function relationship. Their in-depth review of the subject identifies benefits in prevention rather than treatment of psychoses. Lena Burri and Kjetil Berge presents evidence in favor of marine phospholipids associated with astaxanthin as vector for omega-3 fatty acids in supporting cardiovascular and brain health; the identification of the endocannabinoid system and its modulation by omega-3 phospholipids opens doors to therapeutic potential. Asim Duttaroy, and Sanjay Basak reviews the critical aspects of the control of angiogenesis and discusses the peculiar properties of DHA to stimulating it in first trimester placental cells via increased synthesis of VEGF (whereas other fatty acids do not affect its expression) and, from there, the critical importance of DHA in (pre)pregnancy. Eric Lien gathers accumulating evidence in favor of health benefits (vision, resistance to respiratory diseases) associated with the non-discontinuation of dietary supplementation of DHA after the first 6 months of life. Olaf Christophersen questions the reason for the presence of high proportions of DHA in testes, retina, and brain, and extends on the critical importance of the omega-6/3 ratio in keeping germline cell mutation rates under control.

On the Market behind the economics of the omega-6/3 fatty acids, Jack Winkler starts with an appropriate definition of sustainability: “securing regular supplies of LC-Omega-3 sufficient to meet the nutritional needs of the global population.” He goes on estimating the nutrition gap from reviewing sourcing and from there perceives an urgent need for rationing and incrementing, pragmatically. Simeon Hill reveals current lack of knowledge—and therefore area of uncertainty—in how natural state of ecosystems does or may respond to exploitation. Taking Antarctic krill fishery as an example, he identifies the need for precautionary measures and responsible governance to serve sustainability. Jesse Trushenski and John Bowzer add promising perspectives in terms of harnessing the biosynthetic capacity of cultured fish to produce/deposit LC-PUFA in their tissue and, in that respect, the positive influence of noncompeting dietary saturated fats versus linoleic acid. Thomas Balle tells us about the capacity of the industry to enzymatically process omega-3 oil to highly concentrate forms, hence keeping pace with the growing markets of dietary supplements. Peter Lembke has a similar endgame objective with non-enzyme-based processes, i.e., supercritical fluid extraction and molecular distillation, resulting in outstandingly pure omega-3 oils. Kirsten Kramer and coworkers elaborate on current and developing technologies to accurately measure EPA and DHA in omega-3 oils. Clearly, the highly standardized GC remains gold, but

a high-throughput IR methodology is well on its way to cope with the growing demand for analyses. Michael Schneider rebounds on marine phospholipids as new generation of omega-3 fatty acids with high potential of market development for they outperform marine triglycerides in terms of their natural content of omega-3, their stability versus oxidation, their diet-to-tissue transfer, and their therapeutic potential. Wayne Coates reviews plant sources of alpha-linolenic acid and their contribution to the pool of LC-Omega-3 in humans or more broadly speaking to the economics of omega-6/3. Finally, Nigel Baldwin looks at the regulatory and labeling challenges—health claims—for omega-3 oils and derived products. In summary the books focuses on four key principles from international meetings reviewed in Chap. 1:

Brain and heart disorders resulting from LC-Omega-3 (EPA+DHA) deficiency are the biggest challenges to the future of humanity. Their associated costs are currently bankrupting health care systems and threatening wider economic instability worldwide.

Tissue concentrations of LC-Omega-3 (relative to LC-Omega-6) are the key variable for health—not dietary intakes. Thus biomarkers need to be standardized and used as public health targets and omega-3 Index 8–11, Omega-3 in HUFA 50%+ would protect 98% of the population.

Dietary intake of >1,000 mg LC-Omega-3 needed if consuming Western-type diet (but this depends on dietary %LA vs. ALA and ARA) as most people fall far short of these basic needs.

Shorter-chain omega-3 (ALA, SDA and EPA) have poor conversion to DHA in humans.

In conclusion the chapters support international conference and experts recommendations for action as to make tissue targets feasible, we urgently need to:

- Reduce LA and increase ALA in human and animal diets.
- Increase the availability of LC-Omega-3 (especially DHA) for human consumption in a sustainable, environmentally responsible way.

Finally the book's and authors' key objective is to provide knowledge for the readers' education, key to achieving these changes.

Famenne, Belgium
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Fabien De Meester
Ronald Ross Watson

About the Editors



Dr. Adrienne Bendich has recently retired as Director of Medical Affairs at GlaxoSmithKline (GSK) Consumer Healthcare where she was responsible for leading the innovation and medical programs in support of many well-known brands including TUMS and Os-Cal. Dr. Bendich had primary responsibility for GSK's support for the Women's Health Initiative (WHI) intervention study. Prior to joining GSK, Dr. Bendich was at Roche Vitamins Inc. and was involved with the groundbreaking clinical studies showing that folic acid-containing multivitamins significantly reduced major classes of birth defects. Dr. Bendich has coauthored over 100 major clinical research studies in the area of preventive nutrition. Dr

Bendich is recognized as a leading authority on antioxidants, nutrition and immunity and pregnancy outcomes, vitamin safety and the cost-effectiveness of vitamin/mineral supplementation.

Dr. Bendich, who is now President of Consultants in Consumer Healthcare LLC, is the editor of ten books including "**Preventive Nutrition: The Comprehensive Guide For Health Professionals, Fourth Edition**" coedited with Dr. Richard Deckelbaum, and is **Series Editor of "Nutrition and Health"** for Springer/Humana Press (www.springer.com/series/7659). The Series contains 40 published volumes—major new editions in 2010–2011 include **Vitamin D, Second Edition** edited by Dr. Michael Holick; "**Dietary Components and Immune Function**" edited by Dr. Ronald Ross Watson, Dr. Sherma Zibadi and Dr. Victor R. Preedy; "**Bioactive Compounds and Cancer**" edited by Dr. John A. Milner and Dr. Donato F. Romagnolo; "**Modern Dietary Fat Intakes in Disease Promotion**" edited by Dr. Fabien De Meester, Dr. Sherma Zibadi, and Dr. Ronald Ross Watson; "**Iron Deficiency and Overload**" edited by Dr. Shlomo Yehuda and Dr. David Mostofsky; "**Nutrition Guide for Physicians**" edited by Dr. Edward Wilson, Dr. George A. Bray, Dr. Norman Temple and Dr. Mary Struble; "**Nutrition and Metabolism**" edited by Dr. Christos Mantzoros and "**Fluid and Electrolytes in Pediatrics**" edited by Leonard Feld and Dr. Frederick Kaskel. Recent volumes include: "**Handbook of Drug-Nutrient Interactions**" edited by Dr. Joseph Boullata and Dr. Vincent Armenti; "**Probiotics in Pediatric Medicine**" edited by Dr. Sonia Michail and Dr. Philip Sherman; "**Handbook of Nutrition and Pregnancy**" edited by Dr. Carol Lammi-Keefe, Dr. Sarah Couch and Dr. Elliot Philipson; "**Nutrition and Rheumatic Disease**" edited by Dr. Laura Coleman; "**Nutrition and Kidney Disease**" edited by Dr. Laura Byham-Grey, Dr. Jerrilynn Burrowes and Dr. Glenn Chertow; "**Nutrition and Health in Developing Countries**" edited by Dr. Richard Semba and Dr. Martin Bloem; "**Calcium in Human Health**" edited by Dr. Robert Heaney and Dr. Connie Weaver and "**Nutrition and Bone Health**" edited by Dr. Michael Holick and Dr. Bess Dawson-Hughes.

Dr. Bendich served as Associate Editor for “Nutrition” the International Journal; served on the Editorial Board of the Journal of Women’s Health and Gender-Based Medicine, and was a member of the Board of Directors of the American College of Nutrition.

Dr. Bendich was the recipient of the Roche Research Award, is a *Tribute to Women and Industry* Awardee and, was a recipient of the Burroughs Wellcome Visiting Professorship in Basic Medical Sciences, 2000–2001. In 2008, Dr. Bendich was given the Council for Responsible Nutrition (CRN) Apple Award in recognition of her many contributions to the scientific understanding of dietary supplements. Dr Bendich holds academic appointments as Adjunct Professor in the Department of Preventive Medicine and Community Health at UMDNJ and has an adjunct appointment at the Institute of Nutrition, Columbia University P&S, and is an Adjunct Research Professor, Rutgers University, Newark Campus. She is listed in Who’s Who in American Women.



Dr. Fabien De Meester (50), Ph.D., was until 2007 the President & CEO of the Luxembourg-based family-owned group BNLfood (www.bnlfood.com), formerly Belgian-based Belovo SA, Egg Science & Technology. The brand ‘Belovo’ stands for ‘Belgian Egg’ (Latin translation).

Under his leadership, the group specialized itself in the fractionation of eggs into value-added ingredients for the Food, Infant Food, Cosmetic and Pharmaceutical Industries, and developed the Columbus & OvoLife Concepts (www.columbus-concept.com & www.ovolife.eu), programs that pioneers “wild-type lipid nutrition”, i.e. balanced dietary/plasma essential fatty acid ratio and healthy dietary/blood cholesterol. On 1st May 2009, he decided to step down from d2d management at BNLfood and to create his own venture, DMF (www.dmfrontiers.com), to further develop and promote his vision on the market. His goals and strategy are to catalyse sustainable changes in the Egg/Food Industry towards the inception of a modern Science- & Technology–led Business in the Global Economy. Recreationally, he also develops an international network of highly qualified free thinkers to help Humanity progress towards the Truth (www.tsimtsoum.net).

Dr. De Meester has a PhD in Protein Chemistry from the University of Liège (ULg) in Belgium. He was a Post-Doctoral Fellow at the Weizmann Institute of Science (WIS) of Israel where he specialized in Molecular Biology. Then, he returned to Belgium, studied for an Executive Master Degree in General Management (CEPAC) at the Solvay Business School (SBS) and finally joined the family company at the age of 30 where he initially led the Research-Development-Production departments while reshuffling the management of the company onto modern ISO-standards. In early 99, upon retirement of his father, he became the President & CEO of the Belovo company and on 1st January 2006 the international BNLfood group was established.

Dr. De Meester has published over 50 peer-reviewed research articles, 5 books, 5 patents and has delivered international communications on topics related to Organic Chemistry, Enzymology, Biochemistry, Molecular Biology, Food Science & Business. He has organized a series of international workshops on the Columbus Concept & has recently

launched a 2-D TsimTsoum Concept of holistic health that studies body-mind interactions at chronobiological level.



Ronald R. Watson, Ph.D., attended the University of Idaho but graduated from Brigham Young University in Provo, Utah, with a degree in chemistry in 1966. He earned his Ph.D. in biochemistry from Michigan State University in 1971. His postdoctoral schooling in nutrition and microbiology was completed at the Harvard School of Public Health, where he gained 2 years of postdoctoral research experience in immunology and nutrition.

From 1973 to 1974 Dr. Watson was assistant professor of immunology and performed research at the University of Mississippi Medical Center in Jackson. He was assistant professor of microbiology and immunology at the Indiana University Medical School from 1974 to 1978 and associate professor at Purdue University in the Department of Food and Nutrition from 1978 to 1982. In 1982 Dr. Watson joined the faculty at the University of Arizona Health Sciences Center in the Department of Family and Community Medicine of the School of Medicine. He is currently professor of health promotion sciences in the Mel and Enid Zuckerman Arizona College of Public Health.

Dr. Watson is a member of several national and international nutrition, immunology, cancer, and alcoholism research societies. Among his patents he has one on a dietary supplement; passion fruit peel extract with more pending. He had done DHEA research on its effects on mouse AIDS and immune function for 20 years. He edited a previous book on melatonin (Watson RR. *Health Promotion and Aging: The Role of Dehydroepiandrosterone (DHEA)*. Harwood Academic Publishers, 1999, 164 pages). For 30 years he was funded by Wallace Research Foundation to study dietary supplements in health promotion. Dr. Watson has edited more than 100 books on nutrition, dietary supplements and over-the-counter agents, and drugs of abuse as scientific reference books. He has published more than 500 research and review articles.



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Part I
Introduction

1 Introduction: The Economics of Omega-6/3

Fabien De Meester

Scientific evidence keeps accumulating that non-communicable diseases, or NCDs, are avoidable; it is an omega-6/3 ratio¹ away. The perspective of annihilating public health care costs by returning dietary/blood omega-6/3 ratios to their evolutionary standard $\sim 1/1$ is appealing, and devastating at the same time. The double-edge sword represents a unique opportunity for humanity to progress. On the one hand, the money that can be potentially saved on current dead-end medical practices—treatment rather than prevention—is enormous; on the other hand, the money that can be potentially invested in new innovative approaches to human mind ↔ body holistic health needs creativity. It is this change of paradigm—saving money to promote creativity—that requires careful planning and execution. To keep saying things in layman terms, tackling NCDs and health care costs at large is just not good enough; creating jobs through developing new theories that require investigation and confirmation and which result in new large-scale economically sound projects is what it takes.

The need for omega-3 fatty acids is fast increasing—under current sourcing and processing standards a critical situation of global shortage is expected by 2017. Such dooming perspective boosts the economics of alternative (1) sourcing systems, i.e., integrated marine aquacultures and fisheries, genetically modified land-based seeds and plants, plant-based algae fermentation; (2) processing/refining systems, i.e., recovery of industrial fish trimmings, optimizing extraction/refining yields; and (3) diet-tissue transfer, i.e., background diet—composition and timing, synergistic supplementation of humans and their modern marine and land-based husbandries. The rationale behind this multi-alternative sustainable approach to the economics of omega-6/3 was expressed as a common statement at the outset of the 2011 Omega-3 Summit (1).

This book focuses on the heart and the brain, and the roles of long chain (C20-22) omega-6/3 fatty acids in supporting and maintaining their functions. The omega-3 index

¹Provided no other essential nutrients are substantially deviated from their recommended daily intakes. The notion of omega-6/3 ratio has evolved from the time it was first expressed as an evolutionary dietary standard to its contemporary corresponding *blood* fatty acid index and status. This book reviews and refers to those aspects extensively and intensively.

(% of EPA+DHA in red blood cell total fatty acids) keeps accumulating medical credit as a *primary* risk factor—surpassing in reliability the historical *secondary* risk factors-related Framingham score—to assess cardio- and cerebrovascular ill-health. At the same time, the twentieth century’s cholesterol craze keeps falling apart with the past statin trials shedding doubt upon its integrity and a more realistic theory of healthy omega-6/3 cholesterol evolving. At the end of the day, neither cholesterol nor saturated fats are essential nutrients to humans; they could therefore never be *primary* risk factors of NCDs—no matter how much money was and perhaps still is invested at attempting to demonstrate the contrary.

For those who still think or believe that nonessential nutrients—such as cholesterol, saturated and monounsaturated fats, glucose and carbohydrates, and the like, accounting for the bulk (~90%) of the daily energy intake—are primary risk factors in diet-ill health relationships, the best advice to convey probably resides in: “keep reading, evaluating, questioning, arguing, disputing commonly established facts.” As someone once said, “I cannot teach you anything, I can only help you think.” Good points to start from that refreshed perspective are the long-standing, well-documented, evidence-based, unbiased scientific open access site maintained by Uffe Ravnskov² and the more recent yet similarly scholarly blog developed by Michel de Lorgeril.³

It is Artemis Simopoulos who once inspired nutritionists to take a new look at human nutrition, pointing out the evolutionary fact that *Homo sapiens*’ genetic pattern evolved on a diet that was basically balanced in essential fats (Omega-6/3 ~ 1). Michael Crawford came with the hypothesis from earlier observation that free-roaming non-domesticated animals in the African Savannah keep responding to an outspoken evolutionary principle. Such a basic unique principle evidently prevents—if only in humans—against excess body weight and obesity.

Donald McNamara scientifically established the fact that dietary/blood cholesterol was not related to cardiovascular disease (CVD), and Harumi Okuyama concluded that saturated fats were a non-issue unless associated with modern plant/animal fats exceedingly rich in omega-6 fatty acids. William Lands developed mathematical models to predict risk of death from coronary heart disease (CHD) from population-based observational data related to total blood proportion of omega-6 highly unsaturated fatty acids (omega-6 status). Jing Kang engineered fat-1 mice to show that tissues naturally tend in their constant search for “homeostasis” to balance omega-6/3 fatty acid composition in cell membranes. Claudio Galli developed a reliable bench methodology for fatty acid analyses of blood collected from fingertips whereupon William Harris and Clemens von Schacky went on deriving a complementary clinical approach (omega-3 index) based on fatty acid analyses in red blood cells.

The Columbus Concept⁴ (2) was born: by which it is hypothesized that the most single common roots of all chronic degenerative diseases causing 85% of all deaths

²<http://www.ravnskov.nu/uffe>

³<http://www.michel.delorgeril.info>

⁴The Columbus Concept (<http://www.columbus-concept.com>) emanates from a research project initiated in 1995 in a family-owned egg-processing company located in Belgium, in yet another 2nd World War (sadly) famous town, Bastogne, in the Ardennes Region (http://en.wikipedia.org/wiki/Mardasson_Memorial). The Battle of the Bulge has left the place with scars and opportunities for Humanity to progress. A pioneer in Egg Science & Technology, the family company surely was, for two generations, of the De Meester family. Eventually, the brands remain: Belovo, Columbus, OvoLife, BNLfood (<http://www.bnlfood.com>).

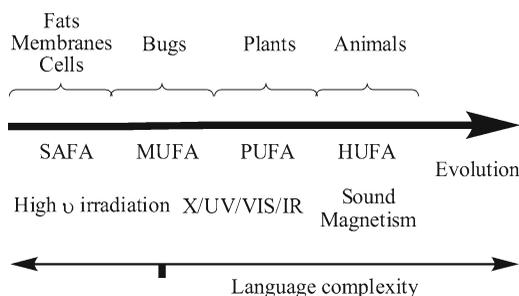


Fig. 1.1. Cell membrane fatty acids from an evolutionary perspective. The environmental slow—allowing for reversible adaptation—yet irreversible continuous decrease in energy enforces an evolutionary pathway whereby cell membrane captors (fatty acids) must continuously reduce their detection threshold, i.e., through increasing carbon chain length and number of alkyl allenes (allylic double bonds). *SAFA* saturated fatty acids, *MUFA* monounsaturated fatty acids, *PUFA* polyunsaturated fatty acids, *HUFA* highly unsaturated fatty acids.

worldwide is an eicosanoid-derived uncontrolled inflammatory process at tissue level, “The Tissue is The Issue,” and that a return to the original balanced (1:1) ratio of polyunsaturated fatty acids (PUFAs) and/or to a corresponding 25% proportion of ω (omega)6 highly unsaturated fatty acids (HUFAs) in plasma/serum total lipids (ω [omega]6: ω [omega]3 PUFAs = 1:1 and/or % ω [omega]6 in HUFAs = 25) can possibly reduce the risk of developing chronic degenerative diseases to near zero at population level.

The Chronomics Trial test-validates the evolutionary diet/tissue hypothesis from a broadened psychosomatic approach recognizing the importance of the mind stress \leftrightarrow body strain response in the biological cascade leading to tissue injury, which if not taken care of at the level of cell membrane fatty acids eventually transforms into chronic inflammation and the inception of NCDs.

As science progresses, however, it appears that fatty acids play or may play roles that so far remain unknown. From an evolutionary perspective, surely their potential involvement in chronobiology (allylic double bond), pharmacology (green-lipped mussel isomers) and speciation (very long chain fatty acids), deserves serious (re)investigation (Fig. 1.1). (See Chap. 22 of this book: “From *Columbus* to *TsimTsoum* Concepts: a Kyoto-type Approach” for a perspective in that direction.)

Even more intriguing are the potential activities of the *absents*—i.e., some isomers of plant (ALA/SDA: C18:3/4w3, GLA/DHGLA: C18/20:3w6) and of animal (ETA: C20:4w3, DPA: C22:5w6) origins (Fig. 1.2)—which under normal circumstances do appear barely or not at all in red blood cells yet may accumulate in circulating triglycerides and body fats and/or exhibit powerful biological and physiological activities upon ingestion. They should perhaps be reassessed from such refreshed perspective. From a pure mechanistic perspective, it is of most interest that omega-6/3 fatty acids do not dispute allylic double bond representation at tissue level, i.e., fatty acids with 2 and 4 allylic double bonds are of the omega-6 family, fatty acids of 3, 5, and 6 allylic double bonds are of the omega-3 family. (The mechanistic perspective, which most probably explains why the 6 allylic double bonds omega-3 fatty acid (DHA) has selectively surpassed its sequentially logical omega-6 isomer (DPA), is also given in Chap. 22 of this book.)

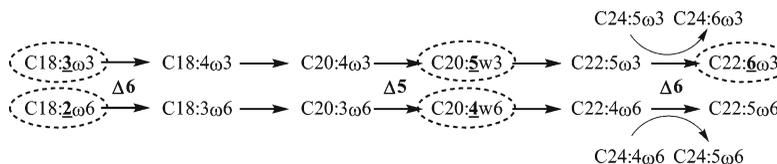


Fig. 1.2. Omega-6/3 fatty acids and their representation at tissue level. Note the sequential interchange between the two families as the number of allylic double bonds increases. It is this number (i.e., the number of allylic double bonds) that appears to represent the selective advantage, not the fatty acid per se.

There are also those very long chain highly unsaturated fatty acids (>C22) that start to show up in cognitive tissues of most advanced species. The reason of their being still needs to be deciphered and elucidated, but their involvement in the next quantum leap of evolution makes little doubt: The more evolved a species, the longer its cell membrane fatty acids and the higher its number of allylic double bonds—this just appears as an entropic condition to species adaptation to ever lower energy environments. If one takes that past jump from plant to animal kingdoms as a possible adaptive pattern for future evolutionary steps, one can envision the next jump up the ladder upon adaptation of cognitive systems to low energy / frequency communicative systems (Fig. 1.1). In fact, some of us may have already started to experience uncommon ways of communicating—sometimes erroneously referred to as hallucinations—which obviously bring upon new selective sociopsychological advantages.

Similarly, the ancestor short chain (C18) may still very well play a similarly crucial role at mind↔body frontiers; how much effort is currently spent on cosmetics to help humans keep their hair and skin healthy-looking, for them to just keep self-esteem and to strive for the best in life? Yet, alpha-linolenic acid (C18) has been used for ages in pet foods for the very same recognized purpose...or was it for human eyes' satisfaction only?

The current battle for fame and recognition between long and short chain omega-3 fatty acids is an artifact of the still current inability of humans to approach human medicine from a holistic perspective. And it is far from evident that the body-oriented modern medicine of the West has protected humans from NCDs, no matter how salutary it appears to have been, and obviously is, on the acute and/or communicable sides. The hope resides in the opportunity for omega-6/3 fatty acids to open a door to an evidence-based holistic approach to health. The TsimTsoum Institute⁵ (3) militates in that refreshing direction initially set for by the Columbus Institute (4). Chapter 22 of this book attempts to formulate a possible avenue of future development in the field.

FROM LANDS MATHEMATICAL MODEL TO THE DEFINITION OF AN ADEQUATE INTAKE

The evolutionary diet/tissue hypothesis (2), i.e., that a return to the original balanced (1:1) ratio of polyunsaturated fatty acids (PUFAs) and/or to a corresponding 25% proportion of ω(omega)6 highly unsaturated fatty acids (HUFAs) in plasma/

⁵ <http://www.tsimtsoum.net>

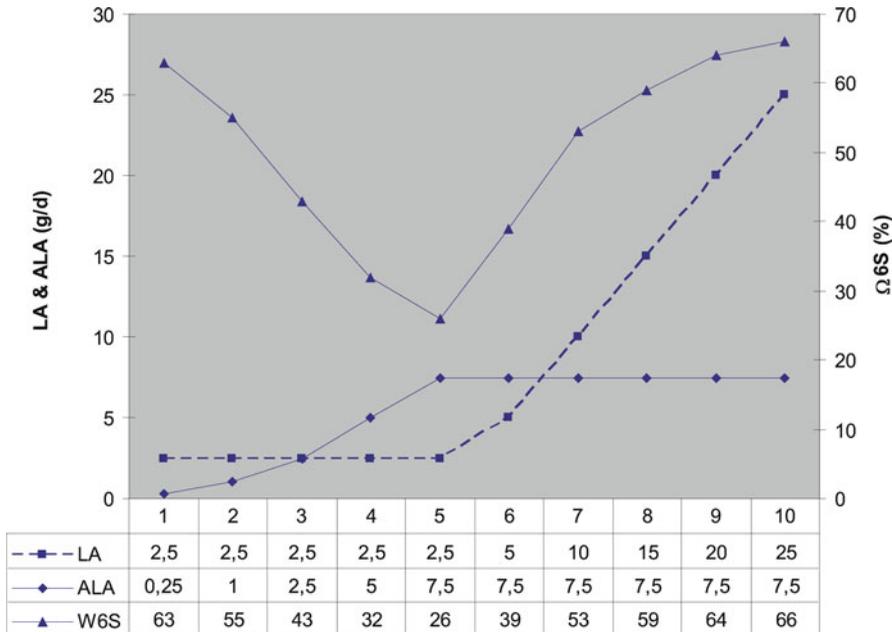


Fig. 1.3. Diagram depicting the evolution of the Omega-6 Status ($\Omega 6S$) in total blood lipids as a function of varying contributions of LA and ALA in a typical vegan/vegetarian diet: 2,250 cal/day; 65 g/day fat (585 cal, 26en%). Ten different patterns are shown; starting from pattern #5 with 2.5 g/day LA and 7.5 g/day ALA and an $\Omega 6S \sim 25\%$, then on the right-hand side LA increasing from 2.5 to 25 g/day and on the left-hand side ALA decreasing from 7.5 to 0.25 g/day, showing in both scenarios an $\Omega 6S$ steadily increasing from $\sim 25\%$ to $\sim 65\%$.

serum total lipids ($\omega[\text{omega}]6:\omega[\text{omega}]3$ PUFAs=1:1 and/or $\% \omega[\text{omega}]6$ in HUFAs=25) (4) can possibly reduce the risk of developing chronic degenerative diseases to near *zero* at population level, allows to estimate from Lands mathematical model that a vegan/vegetarian diet containing PUFA in the form of solely plant-derived linoleic acid (LA) and alpha-linoleic acid (ALA) in a 1-to-3 ratio would suffice to reach and maintain the evolutionary standards (Fig. 1.3). To say it otherwise, there is no need per se of HUFA of any sort to adjust the blood total lipids omega-6 status of 25%. In an omnivorous diet whereby egg, meat, and animal-derived arachidonic acid (AA) is introduced even at such a low level of ~ 100 mg/day (the equivalent of one standard egg a day), the omega-6 status in total blood lipids reaches $\sim 30\%$ at a LA:ALA ratio of 1:3 (Fig. 1.4).

Increasing the amount of LA and AA to levels characteristics of modern Western type diets (i.e., 20–25 g/day LA, 400–600 mg/day AA) translates into omega-6 status values ranging from 80 to 90% almost irrespective of the g/day contribution of ALA in the diet (Fig. 1.4). The biochemical fatty acid pathways are just over-saturated and entirely guided by omega-6s.

Another way to look at the critical interplay connecting dietary PUFA to blood omega-6 status is through the representation of the trends in daily needs of omega-3 HUFA needed to take the omega-6 status back to $\sim 25\%$ under the various dietary lipid patterns just discussed. It then appears then that omega-3 HUFAs are in fact conditionally

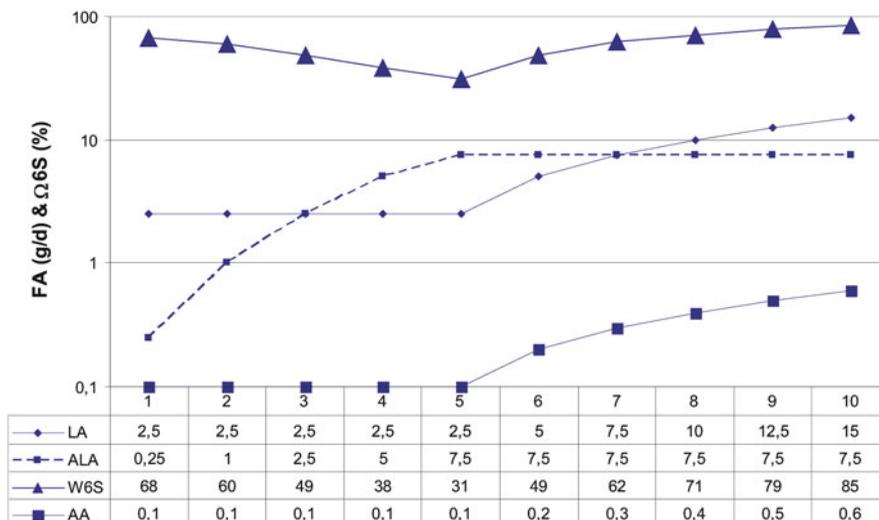


Fig. 1.4. Diagram depicting the evolution of the Omega-6 Status ($\Omega 6S$) in total blood lipids as a function of varying contributions of LA and ALA in a typical omnivorous diet: 2,250 cal/day; 65 g/day fat (585 cal, 26en%). Ten different patterns are shown; starting from pattern #5 with 2.5 g/day LA, 0.1 g/day AA and 7.5 g/day ALA and an $\Omega 6S$ ~30%, then on the right-hand side increasing LA from 2.5 to 25 g/day with AA increasing from 0.1 to 0.6 g/day and on the left-hand side decreasing ALA from 7.5 to 0.25 g/day with AA kept constant at 0.1 g/day, showing an $\Omega 6S$ steadily increasing to ~85% and ~70%, respectively.

essential to humans, becoming ever more essential as the dietary intake of omega-6 PUFA (LA) and/or omega-6 HUFA (AA) increases. A vegan/vegetarian diet with the Western standard of 8–12 en%LA requires some 6.75 g/day omega-3 HUFA (Fig. 1.5), whereas its similar omnivorous standard including some 400–600 mg AA may require up to 10 g omega-3 HUFA (Fig. 1.6) daily to maintain an omega-6 status of 25%.

From these mathematical computations, it is also reckoned that the conversion of ALA to omega-3 HUFA at 2.5 g/day LA is $9 \pm 1\%$, whereas it reduces to 8–8.5% at 2.5 g/day LA + 0.1 g/day AA. Independent evidence tends to show that the amount of DHA that may be produced from ALA conversion remains low (<1%) so perhaps it is of importance to emphasize that the conversion rates reckoned here from Lands' model addresses total omega-3-HUFA, and not any omega-3-HUFA in particular.

FATTY ACID EVOLUTIONARY STANDARDS AND RISKS OF CHRONIC DISEASES

From his biochemical observations and mathematical model, Lands went on to analyze observational data available at population levels worldwide (5). Heart attack death rate (per 100,000 inhabitants) does show a strong linear dependence on the proportion of omega-6 HUFA in total blood HUFA, i.e., the omega-6 status ($\Omega 6S$) (5). More recently, the Chronomics Study (6) did reveal a similar relationship between the ratio of

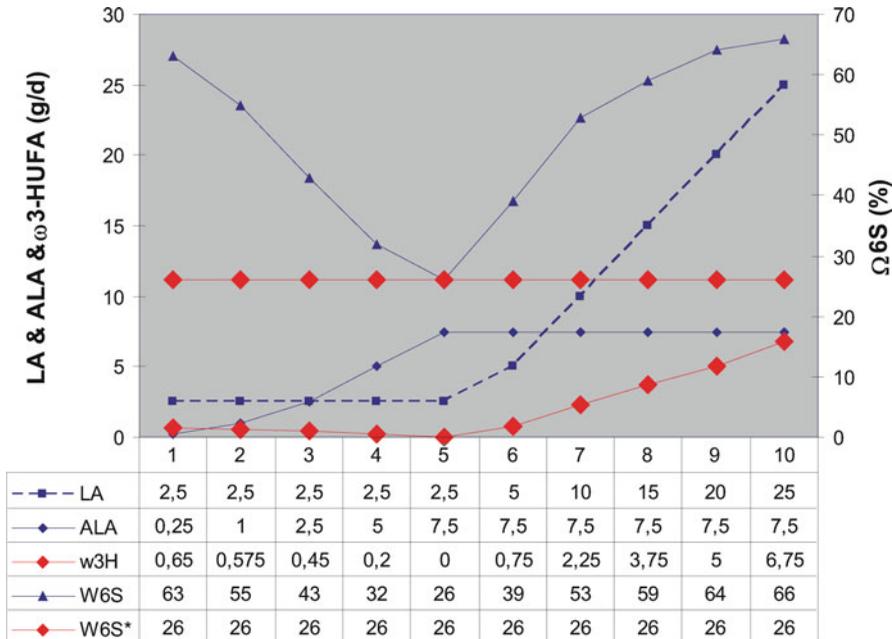


Fig. 1.5. Diagram depicting the trend of omega-3 HUFA needed daily to correct the Omega-6 Status ($\Omega 6S$) back to $\sim 25\%$ in total blood lipids as a function of varying contributions of LA and ALA in a typical vegan/vegetarian diet: 2,250 cal/day; 65 g/day fat (585 cal, 26en%). Ten different patterns are shown; starting from pattern #5 with 0 g/day omega-3-HUFA, then on the right-hand side increasing from 0 to 6.75 g/day and on the left-hand side increasing from 0 to 0.65 g/day, showing in both scenarios an $\Omega 6S$ steady at $\sim 25\%$.

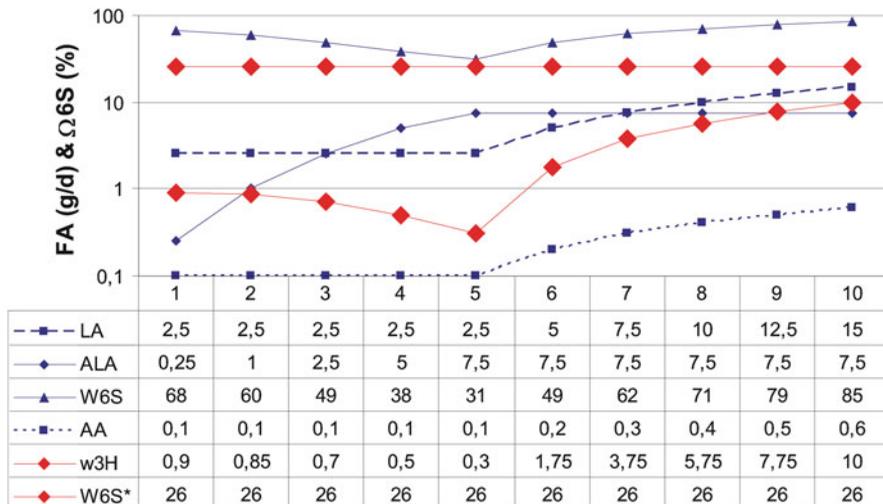


Fig. 1.6. Diagram depicting the trend of omega-3 HUFA needed daily to correct the Omega-6 Status ($\Omega 6S$) back to $\sim 25\%$ in total blood lipids as a function of varying contributions of LA, AA and ALA in a typical omnivorous diet: 2,250 cal/day; 65 g/day fat (585 cal, 26en%). Ten different patterns are shown; starting from pattern #5 with 0.5 g/day omega-3-HUFA, then on the right-hand side increasing from 0.5 to 10 g/day and on the left-hand side increasing from 0.5 to 0.9 g/day, showing in both scenarios an $\Omega 6S$ steady at $\sim 25\%$.