

## Welcome to ACTI-Day Nutrition and Health Conference 2008

Functional and Nutritional foods are an established and growing market, however it is constantly changing because of new scientific findings and evolving consumer needs.

ACTI-Day Nutrition and Health Conference is dedicated to nutrition & health claims. Today you will get an overview of market trends, discover new examples of food formulation with improved nutritional value, get updated about the regulation, discuss about the latest scientific evidence in health topics such as gut health, satiety and immunity, and benefit from expert knowledge.

During ACTI-Day, we wish to offer you new technical, scientific and marketing perspectives, and let you find out how innovative ingredients can help you take an active part in the market of nutritional and healthy food.

# ACTI-Day Nutrition & Health Conference

September 25<sup>th</sup> 2008, Paris Charles de Gaulle

## **Expert Speakers**

Prof. Philip Calder, University of Southampton, UK  
Prof. Marc Fantino, University of Burgundy, France  
Ms Céline Hurson, SYRAL Marketing Department  
Dr. Jean-Michel Lecerf, Institut Pasteur Lille, France  
Dr. Jean-Charles Martin, INSERM, Marseille, France  
Mrs Carole Midon, SYRAL Customer Technical Support  
Ms Virginia Millan, SYRAL Customer Technical Support  
Prof. Robert Rastall, University of Reading, UK  
Ms Frédérique Respondek, SYRAL Innovation Department  
Prof. Daniel Tomé, AgroParisTech, France  
Mrs Kath Veal, Leatherhead Food International, UK

## **In the chair**

Mr Daniel Cochet, SYRAL Marketing Department  
Ms Frédérique Respondek, SYRAL Innovation Department  
Dr. Anne Wagner, SYRAL Innovation Department

## SPEAKERS' PROFILES

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### **Prof. Philip C. Calder, University of Southampton, UK**

Philip Calder is Professor of Nutritional Immunology at the University of Southampton, United Kingdom. He has a Ph.D. in biochemistry from the University of Auckland, New Zealand. He held a Nuffield Medical Fellowship in the Department of Biochemistry, University of Oxford from 1987 to 1991. Professor Calder has been studying the influence of dietary fatty acids on aspects on human health, in particular in relation to cardiovascular disease, inflammation and immunity, since 1987. In 1995 he was awarded the Sir David Cuthbertson Medal by the UK Nutrition Society for this work and he was awarded the Belgian Danone Institute Chair for 2004 and the Nutricia International Award for 2007. Prof. Calder served as an elected member of the Council of the UK Nutrition Society and he served on the Clinical Nutrition and Metabolism Group, Programmes and Publications Committees of that Society. Professor Calder was a founder member of the Nutritional Immunology Group of the British Society of Immunology. He served on the Council and Programmes Committee of the British Association for Parenteral and Enteral Nutrition and on the Scientific Committee of the European Society for Clinical Nutrition and Metabolism (ESPEN). Prof. Calder is Vice-President, and President-Elect, of the International Society for the Study of Fatty Acids and Lipids (ISSFAL). He is Editor-in-Chief of the British Journal of Nutrition and an Associate Editor of Clinical Science and of Lipids. He is a member of the Editorial Boards of different periodical publications. He was founding Editor-in-Chief of the Frontiers in Nutritional Science series of books. Prof. Calder served on the British Nutrition Foundation's Task Force on "Adverse Reactions to Foods" and on ILSI Europe's "Gut Health and Immunity" PASSCLAIM Task Group. He chaired the ILSI Europe Workshops on "Markers to Assess the Impact of Nutrition on Immune Function in Man" and on "The Impact of Nutrition on Inflammation" and he was overall chair of the 6<sup>th</sup> Congress of ISSFAL. Prof. Calder is an EFSA External Expert.

He has published over 150 research papers, over 100 review articles and book chapters, and 25 commentaries.

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### **Prof. Marc Fantino, University of Burgundy, France**

Marc Fantino is a medical doctor and "Docteur ès Sciences". Full professor of medicine, he is "Professeur des Universités - Biologiste des Hôpitaux". Presently, he manages the Department of Human Physiology of the Medical School of the Burgundy University, and he is the head of the Department of Functional Explorations of the University Hospital (CHU) of Dijon (France). For 24 years, he has been an elected member of the "Conseil Scientifique" of the Burgundy University, and from 1993 to 2001 he was the director of the doctoral school of the universities of Burgundy and of Franche-Comté (ED 174). Then, he founded and manages the clinical research organization CREABio<sup>®</sup>, accredited to perform researches on healthy human subjects. He initiated and managed many basic or applied researches in collaboration with numerous food and drug companies.

From 1998 to 2006 he had been a full expert at the French Food Safety Agency (AFSSA) and is still a "peripheral" expert. But since 2004, he is the President of the Committee which labialized educational projects of the National Program Nutrition and Health (PNNS).

Prof. Fantino manages researches in the field of the sensorial and metabolic process which regulate feeding behaviours and fat mass in animals and human subjects. For these works, he developed different behavioural, neurophysiologic or pharmacological approaches and models. In addition, in the field of the epidemiology of nutrition, his team is in charge of the scientific aspects of the surveys on the food intake and the nutritional status of the French infants and toddlers (aged for 1 to 36 months), which were performed every 8 years for 25 years, on a representative sample of the population.

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### **Ms Céline Hurson, SYRAL Marketing Department**

Céline Hurson graduated from the ENSAIA National Agronomy and Food Industry School (Nancy, France) and gained experience in new products development and launching. Since 2006, she has been in charge of communication and marketing for SYRAL. She worked on optimising communication of health claims to consumers and developed scientific communication tools on nutritional ingredients and prebiotics.

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### **Dr. Jean-Michel Lecerf, Institut Pasteur Lille, France**

Jean-Michel Lecerf is a medical doctor, specialized in endocrinology and metabolic diseases, and is a nutritionist. He is physician in the “Centre Hospitalier Universitaire et Régional de Lille”, and has been working for 24 years in the lipid clinic of the Internal Medicine Department. He is associated professor at the “Université des Sciences et Technologies de Lille” and teaches Nutrition.

Since 1982 he is Head of the Nutrition Department of “Institut Pasteur de Lille”.

He is member of many Scientific and Medical Societies, Scientific Committees, Editorial Boards, Expert at the French Food Agency (AFSSA).

He is author of more than 300 papers in medical and scientific journals in the fields of nutrition, metabolism, diabetes, endocrinology and obesity.

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### **Dr. Jean-Charles Martin, INSERM, Marseille, France**

Jean-Charles Martin is a PhD from the University of Tours, France. After his PhD, he moved to Toronto, Canada, for a post-doc in the Banting and Best Department of Medical Research, before being hired by INRA, Dijon, France. He is now carrying out his research in a INSERM/INRA JRU in Marseille. His research interests were primarily dedicated to the effects of dietary fatty acids (long-chain PUFA, milk-fat fatty acids such as conjugated linoleic acids, trans fatty acids, and cyclic fatty acid monomers occurring from fat frying) on health outcomes such as infant nutrition and development, cardiovascular diseases and obesity. He is now developing system biology approaches to evaluate the broad nutritional impact of food components on health, with a special emphasis on metabolomics.

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### **Ms Carole Midon, SYRAL Customer Technical Support**

Carole Midon graduated in Food Sciences & Technology from the ENSAIA, National Agronomy school of Nancy, France in 1999. From 2000 to 2002, she is in charge of QA related files for Kruger France, a commercial subsidiary of the German group Krüger (beverages, foodstuffs and pharmaceutical products in instant form). Then, she becomes Customer support and specifications management, QA for SYRAL - Marckolsheim plant and for Beghin Meiji. Since 2007, she is in charge of the Customer Technical Support team - available throughout Europe, committed to help customers to choose the optimal ingredients to fit specific process and end-product requirements or formulation.

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### **Ms Virginia Millan, SYRAL Customer Technical Support**

Virginia Millan graduated in Chemistry (branch Organic Chemistry) from the University of Zaragoza (Spain). She postgraduated in Environmental Engineering from the Industrial Engineering College, University of Zaragoza and got a Master in Environmental Management from the University of Granada (Spain).

From 1993 to 1996, she was Technical coordinator in "Control Alimentario". This company gave consultancy services to small-medium food companies for quality control, good manufacturing practices, analytical services, legislation issues and personnel training.

Since 1996, she has been Customer Support Engineer Food for Southern Europe in Amylum / Tate&Lyle / SYRAL.

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### **Prof. Robert Rastall, University of Reading, UK**

Bob Rastall is currently Head of the Department of Food Biosciences at the University of Reading in the UK and also holds the post of Professor of Biotechnology. He is also head of the Food and Bioprocessing Sciences Research Group in the department and is joint leader of the University Food Chain and Health research theme. He has a BSc in Applied Biology and a PhD in Microbial Biochemistry (1987) from the University of Greenwich, London. He held research fellowships in the field of carbohydrate bioengineering at the University of Westminster until joining the University of Reading in 1993.

Professor Rastall now leads a personal research team developing novel enzymatic manufacturing technologies for functional carbohydrates targeted at gut health. His research is focused on understanding structure-function relationships in prebiotic carbohydrates and the application of that knowledge to the rational development of functionally enhanced prebiotics. He is also developing concepts around the rational targeting of synbiotics to specific health outcomes.

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### **Ms Frédérique Respondek, SYRAL Innovation Department**

After graduating from ENESAD (National School of Agronomy) with a Masters Degree in Agricultural Sciences specialised in Animal Science, Frédérique Respondek gained experience in research on nutrition in institutes in France and USA and published several articles. She then joined the TEREOS group in 2004 as coordinator of research projects related to fructo-oligosaccharides. She has been supervising studies in animal models and humans, participating to building knowledge around prebiotics, their effects on health and mode of action through modulation of the digestive microflora. Frédérique Respondek is now Scientific Affairs Manager for SYRAL, evaluating the nutritional properties of starches and other ingredients produced from wheat and maize. She is also an expert member of ILSI's task force on Prebiotics.

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### **Prof. Daniel Tomé, AgroParisTech, France**

Daniel Tomé is President of the Life Sciences and Health department of the AgroParisTech, including the most competitive French institutes in the field of applied biology. He is head of the Physiology of Nutrition and Food Behaviour unit of INRA (National French Institute of Agronomic Research). He wrote more than 200 papers in peer review journals. His research interests are Protein, amino acid and energy requirements and metabolism; Endocrine and nutritional regulation of protein turnover, intermediary metabolism, energy metabolism and body composition; Role of protein and energy nutrients in the central control of food intake; Energy nutrient metabolism in the metabolic syndrome; Relations between human nutrition, human health, and nutrition policy. He is a member of the WHO/UNU/FAO/ESNA expert group for the harmonisation of food standards (2005), and of WHO/FAO/UNU expert consultation on protein and amino acid requirements in human Nutrition (2002). He is a member of different national and professional organisations, including Comité interministériel de validation des chartes d'engagements de progrès nutritionnels (since 2007).

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### **Mrs Kath Veal, Leatherhead Food International, UK**

Kath is the Business Manager for the Regulatory Services section at Leatherhead Food International. Kath is a Food Science graduate with previous experience in the food industry and analytical services. She is a qualified UK Trading Standards Officer with 12 years regulatory experience in practical inspection, sampling and food law enforcement. Kath has worked with the UK Food Standards Agency and sat on a national enforcement panel advising on consistency of interpretation of food legislation. Kath's team includes 22 regulatory professionals who advise on global food legislation. Kath has been involved in many conferences both at Leatherhead and external events such as Vitafoods and FIE, often speaking about the European controls regarding claims.

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### **Dr. Anne Wagner, SYRAL Innovation Department**

Dr. Anne Wagner graduated from the University of Strasbourg and got her PhD at the Institut National Polytechnique de Lorraine, France, specialising in biochemical engineering, before studying molecular biology at the University College of Galway (IR). She is now VP Innovation at SYRAL, coordinating new product & process development, product application department and scientific and regulatory affairs.

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## PROGRAMME

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9:00 – 9:30 Participants registration

9:30 – 9:45 Introduction

### • Health claims

9:45 – 10:15 Launching new functional products with health claims: what is on the market? Which issues remain with the new regulation? And what are consumers expecting?

*Mrs Kath Veal, Leatherhead Food International*

10:15 – 10:35 Consumers survey on perception of gut health claims

*Céline Hurson, Marketing Department SYRAL*

10:35 – 10:45 Actilight® film 'Just makes you feel great'

### • Satiety

10:45 – 11:10 Physiological mechanisms of hunger and satiety: new data and impact on behaviour

*Prof. Marc Fantino, University of Burgundy*

11:10 – 11:35 Coffee break

11:35 – 12:00 Effects of proteins on satiety

*Prof. Daniel Tomé, AgroParisTech, Paris*

### • Nutritional formulation

12:00 – 12:40 Ingredients for nutritional improvement: case studies

- Proteins enrichment and fat reduction

- Sugars & energy reduction with maltitol

- Fibre enrichment with prebiotic fibres

*Carole Midon & Virginia Millan, SYRAL Customer Technical Support*

12:40 – 14:00 Lunch

### • Nutrigenomics and obesity

14:00 – 14:30 Metabolic syndrome and obesity: growing threats promoted by modern food habits

*Dr. Jean-Michel Lecerf, Institut Pasteur Lille*

14:30 – 15:00 Studying modulation of gene expression by food diets: nutrigenomics applied to metabolic syndrome

*Dr. Jean-Charles Martin, Inserm, Marseille*

15:00 – 15:25 Benefits of dietary fibres on metabolism regulation. Example of scFOS

*Frédérique Respondek, SYRAL Innovation Department*

15:25 – 15:45 Coffee break

### • Immunity and Nutrition

15:45 – 16:15 Stimulation of immunity through nutrition

*Dr. Philip Calder, University of Southampton*

16:15 – 16:45 The synbiotic approach from science to food formulation

*Dr. Robert Rastall, University of Reading*

16:45 – 17:00 Conclusion

## **Morning session**

Health Claims

Satiety

Nutritional Formulation

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### *Morning session*

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## **Launching new functional products with health claims: what is on the market? Which issues remain with the new regulation? And what are consumers expecting?**

*Mrs Kath Veal, Leatherhead Food International*

The market for functional foods is a challenging area to operate in but getting things right can reap rewards. This presentation will review market trends with product examples and look at sector values, the impact of regulatory barriers will be assessed and the needs of increasingly demanding consumers will be considered.

Functional foods are often sophisticated formulations which can cause conflict with strong consumer trends towards natural products though fortification ingredients do not appear to have a negative connotation in most markets.

Consumers also demand healthy choices and the market has responded with low/no/reduced fat products in particular with similar treatment for the other "bad" nutrients salt and sugar.

The EU Nutrition and Health Claims Regulation has caused concern to much of the food industry and interpretative guidance is slowly emerging to clarify areas of uncertainty. Health claims evaluations are also now underway and the European Food Safety Authority is assisting the Commission with regard to nutrient profiles which will be hugely significant for product positioning.

Not only does a product have to be functional and comply with the law it also has to make sense to a consumer so in conclusion a number claims will be considered from the consumer perspective.

## Consumers survey on perception of gut health claims

*Ms Céline Hurson, SYRAL Marketing Department*

There are different words and expressions that can be used to convey one and only concept of health claim. Wording has been shown to have an influence on consumers understanding and interest and therefore must be chosen carefully. In the case of gut health claims, it seems that communication particularly needs to be adjusted to targeted consumers' culture.

According to SYRAL market observation in Europe (2007), health claims on prebiotic and gut health functionalities of foodstuffs are differing a lot from a country to another. The word "prebiotic" was frequently found in all European countries. In certain countries such as Germany, it was associated to "fibres" or "effect". "Bifidogenic" or "bifidus effect" were commonly found in France, Benelux, Spain and Italy as an alternative to "prebiotic". In the UK, Benelux, Italy and Spain, it was often referred to "stimulating bacteria", being "good" or "beneficial", sometimes "friendly" (UK) within the "gut" or "intestinal flora". The latter was "balanced" or "rebalanced" by prebiotics in the same countries (but to a lower extent in the UK). No such details were given in Germany. When looking at benefits of prebiotics on gut health, it was mostly referred to "digestion" (UK, Germany, France), "transit" (Benelux, France, Spain) or "regularity" (Italy, UK). Words of "well-being" and "digestive comfort" are particularly frequent in France. In Italy and UK, we found physiological vocabulary such as healthy "digestive system" or "bowel/intestinal function".

In collaboration with Leatherhead Food International, SYRAL ran a consumer study to find out about the preferred wordings of health claims related to the prebiotic effect. Online language-specific questionnaires were run in Dec 2007 - Jan 2008 on 4040 respondents in the UK, France, Germany, Netherlands and Italy.

First, we evaluated the impact of 4 health claims attributed to Actilight® on consumers' interest and intention to buy: prebiotic effect, improved intestinal conditions, increased mineral absorption, lipids metabolism. Average marks range between 3.3 and 3.7 on a 1 (very uninterested) to 5 (very interested) scale, fairly similar to intention to buy. Italians are the most interested, while Dutch are the less interested. Women are more interested than men and interest grows with age, particularly for lipids metabolism.

In a 2<sup>nd</sup> step focused on "prebiotic effect" and "improved intestinal conditions" claims, different wordings were evaluated on interest, so that we could compare them and define the most popular ones per country. In the UK, wordings referring to "friendly bacteria" are the most popular, while in Germany, wordings including the presence of "fibres" or "prebiotics" are preferred. In France, Italy and the Netherlands, consumers prefer wordings mentioning the "gut flora" and its "balance" rather than prebiotics or bifidogenic properties, even though these wordings had been frequently observed on the market. These results should be used by food manufacturers to enhance the impact of their health claims.

### Top wordings by country for the prebiotic claim

**UK:** Stimulates the growth of good digestive bacteria, Boosts the friendly bacteria of the gut flora

**France:** Contribue à maintenir l'équilibre de la flore intestinale, Régénère la flore intestinale, Stimule les bonnes bactéries de la flore intestinale

**Germany:** Regt die Darmflora an, Beitrag zu einer ausgeglichenen Darmflora, Stärkt die guten Bakterien der Darmflora

**Italy:** Rafforza la flora intestinale, Contribuiscono all'equilibrio della flora intestinale, Stimola la crescita dei batteri buoni della flora intestinale

**The Netherlands:** Draagt bij aan een evenwichtige darmflora, Verhoogt de goede bacteriën in de darmflora, Stimuleert de groei van goede spijsverteringsbacteriën

## Physiological mechanisms of hunger and satiety: new data and impact on behaviour

Prof. Marc Fantino - CREABio®, Bourgogne University / CHU Dijon (France)

The energy balance and the long term regulation of the body fat mass are mainly achieved by the short term control of the feeding behaviour, meal after meal. But the metabolic and neuro-endocrine conditions which underline the periodical recurrence of hunger and satiety are still not totally identified in spite of several thousand of works on this topic, published for more than 60 years.

### Macronutrients as signalling molecules: the glucostatic theory

About half a century ago, it has been proposed that the central nervous system senses circulating levels of metabolites such as glucose, lipids, aminoacids, and modified feeding according to the levels of those molecules. However, Jean MAER and his team demonstrated, as earlier as in the fifties, that glucose is the main (if not exclusive!) metabolite for this function. According to Jean MAYER, the hunger state and the seeking for food, then the ingestion, occurred when the ability of the central nervous system to oxidize glucose is low [7]. This mechanism has been known for a long time as the “*glucostatic hypothesis*” of the regulation of food intake.

### The delta glucose, a measure of the rate of glucose oxidation

It is noteworthy that hunger and feeding behaviour do not depend on the absolute glycaemia, but on the ability of the central nervous system to use glucose to provide for its own energy needs. This ability can be quantified by what Jean MAYER called DELTA GLUCOSE [8]. The delta glucose is the difference between glycaemia in the arterial blood reaching the brain, and glycaemia in the venous blood leaving the brain. This difference, combined with the blood flux through the brain, gives the amount of glucose oxidized by the central nervous system at a given time.

MAYER and his collaborators observed that, whatever the model (rat, dog, monkey, human...) and the physiological or physio-pathological state are, when a subject is satiated, the  $\Delta$ -glucose is high (i.e. brain oxidizes a large amount of glucose). Reciprocally, as soon as the  $\Delta$ -glucose decreased and tends to zero, hunger and feeding behavior resume.

Although this classical model of the physiological control of food intake has often been questioned, it is of note that, from an epistemological point of view, glucose being the main energy supply for the brain, and since the glucose stocks are rather low in living organisms, available glucose is quickly oxidized contrary to the lipids which are available in very large amount. So lipids (fatty acids) may not play a similar role as glucose in the short term regulation of food intake. However, several very recent works may seriously question this opinion.

### The glucostatic hypothesis challenged

For decades progress in the knowledge in the field of the regulation of the feeding behaviour mainly concerned the identification of the neuronal network involved, the characterisation of the chemical mediators in the central nervous system (amines, orexigenic or anorexigenic peptides...), or the characterisation of the peripheral messengers which signal to the brain the body fat mass (leptine) or the gut content (CCK, ghrelin...). Surprisingly, in 2002, OBICI and col. (from ROSSETTI's group) reported that central administration (ICV) of oleic acid (OA) inhibits peripheral glucose and insulin production, and drastically decreases food intake [12].

They also showed that the esterification of long chain fatty acids (LCFAs) to LCFA-CoAs is an obligatory step for the hypothalamic action of LCFAs on feeding behaviour. In addition the anorectic effects of OA are mainly exerted on the arcuate nucleus (ARC), where mRNA expression of the orexigenic peptides AgRP and NPY was decreased. Conversely, expression of the anorexigenic peptide POMC was not affected by OA, indicating that the anorectic action of LCFAs is mediated by a specific inhibition of the orexigenic neuropeptides. ARC is recognized as a primary hypothalamic nucleus involved in the physiological regulation of food intake as a fuel gauge area.

### **A physiological role of hypothalamic de novo fatty acid synthesis on food intake regulation**

These observations raise the question of a possible ability of the central nervous system to sense the availability of lipids as well as glucose for the modulation of the food intake, and the authors proposed that lipids may be a key part of a central fuel-sensing mechanism [11]. However the true origin of the intracerebral LCFA, for this function, is puzzling. Fatty acids are derived either from the diet (from the periphery) or by local de novo synthesis. A peripheral origin does not seem essential since it has been shown that only a very small portion of the circulating free fatty acids (~6%) crosses the blood-brain barrier and reaches the cerebrospinal fluid [1]. In addition, the LCFAs are poorly oxidized by the neurons [9]. The local de novo synthesis of LCFA is a common cytosolic process in the ARC neurons, which is highly active when the citric acid cycle in the mitochondria and the oxidation of glucose produce sufficient amount of the three required substrates: NADPH, ATP and acetyl-CoA. Indeed, the generation of new fatty acids in the neurons is actually heavily dependent on the metabolism of glucose to produce these necessary substrates [13]. The central enzyme for the de novo fatty acid synthesis is *fatty acid synthase*, which generates palmitate from a key substrate, *malonyl-CoA*. Malonyl-CoA is generated from acetyl-CoA and CO<sub>2</sub> by *acetyl-CoA carboxylase* (ACC), which activity may be regulated by alteration of its phosphorylation state (it is inactive when phosphorylated). The reverse reaction is catalysed by *malonyl-CoA decarboxylase* (MDC), also regulated by its phosphorylation state (active when phosphorylated).

So, the level of malonyl-CoA is highly dependent on the activity of these three enzymes. Particularly important, numerous recent works indicate that all the pharmacological, genetic or viral manipulations of the activity of these enzymes which increase the amount of intracytoplasmic malonyl-CoA in the ARC neurons, up-regulate anorexigenic peptides (POMC, CART...), down-regulate orexigenic peptides (AgRP and NPY), and accordingly suppress food intake, decrease body weight, and even normalize the weight of genetically obese mice *ob/ob* (review in [3, 6, 17, 18, 19]). Conversely, reduction of malonyl-CoA levels by virus-mediated gene transfer to MCD into hypothalamus of rats results in increased food intake and progressive weight gain [2, 4]. Moreover, high levels of malonyl-CoA inhibit the ability of CPT1 to import fatty acyl-CoAs into mitochondria for oxidation [16].

All these recent data suggest that malonyl-CoA could act in hypothalamus as signalling as well as metabolic intermediate. *De novo* fatty acids synthesis in ARC neurons does not generate LCFAs as oxidizable metabolites, but as *signalling molecules* to regulate food intake: malonyl-CoA acts as a *satiety messenger*. Actually, and the most important, is that the generation of new fatty acid molecules is, as already indicated, heavily dependent on the metabolism of glucose: the main point of pathway regulation occurs at ACC and MDC level.

### **AMP/ATP ratio and AMP-activated protein kinase (AMPK): the cellular fuel gauge in the hypothalamus**

The downstream component of this regulatory pathway is a protein kinase cascade. The activities of ACC and MDC are allosterically regulated by phosphorylation by *AMP-activated protein kinase* (AMPK) [5, 20]. Activation of AMPK requires its own phosphorylation on threonine 172 that occurs when the cellular AMP/ATP ratio increases.

Fasting increases AMPK activity in several hypothalamic areas, (among them ARC) while refeeding inhibits it [10]. When the intra mitochondrial oxidation of glucose weakens, the production of ATP decreases, then activated AMPK phosphorylates and inhibits ACC, while it phosphorylates but activates MDC; that results in a decreased in the hypothalamic levels of malonyl-CoA: satiety vanishes and hunger and food intake resume to restore supplying the brain with glucose.

### **Glucose, still the main energy metabolite in the fuel gauge process**

On the whole, the data above demonstrate that LCFAs participate to the regulation of the food intake as signalling molecules rather than as energy substrates. Such a role is totally in accordance with the glucostatic theory which attributes to glucose a main function (as energy metabolite) in the fuel sensing process in ARC (and/or in other hypothalamic nucleus) at the origin of the neural process which regulates feeding by hunger/satiety alternation.

Further proofs of the predominant role of glucose oxidation will be given with two examples of feeding conditions that sustained glucose oxidation during the post prandial period and delayed hunger recurrence, next meal initiation and decreased food intake at the next meal: enrichment of the previous meal with medium chain triglycerides [14, 15], or with a low glycaemic index starchy foods.

### **Conclusion**

In conclusion, neurons of specific hypothalamic area (including in the ARC) function as fuel gauge to monitor peripheral energy status and produce signals to adjust food intake (and energy expenditure) in order to maintain homeostasis. Even if the molecular mechanism of this complex regulatory process involves intermediates of the fatty acids metabolism as signalling intermediaries, a high level of glucose oxidation still appears as the main initial process that generates and sustains the satiety state.

References available upon request

## Effects of proteins on satiety

*Prof. Daniel Tomé, AgroParisTech, Paris*

It is currently established that under most conditions protein is more satiating than the isoenergetic ingestion of carbohydrate or fat in animals and humans and that a high-protein diet most frequently improves weight loss and body composition.

A high-protein load leads to a higher decrease of energy intake at the next meal than carbohydrate and fat. In the short term preload paradigm, a test-meal is provided to subjects after a delay following the ingestion of the preload. Different preload approaches are used that vary in the nature of the preload (total energy content, macronutrient composition, amount and type of protein, solid or liquid form), in the delay between the preload and the test-meal (spontaneous or fixed delay, duration of the fixed delay), in the nature and composition of the test-meal offered to subject and in the existence or absence of previous adaptation of the subjects to the preload paradigm. A protein-enriched diet induces satiety, improves body composition and results in weight loss. This effect was however modulated by the ratio between carbohydrate and fat and by the type of the protein.

Several mechanisms are candidate signals for protein-induced satiety. At the peripheral level, proteins induce the release of anorexigenic gut hormones CCK, GLP-1 and PYY. Energy expenditure and glucose are probably involved as metabolic signals. Moreover, there is some evidence that the circulating level of amino acids and particularly leucine could impact food intake. Leucine modulates the activity of the energy and nutrient sensor pathways controlled by AMPK and mTOR in the hypothalamus. At the brain level, two afferent pathways are involved in protein and amino acid monitoring: the indirect neuro-mediated (mainly vagus-mediated) and the direct blood pathways. High-protein diets lead to activation of the noradrenergic/adrenergic neuronal pathway in the NTS and in melanocortin neurons in the ARC.

## **Ingredients for nutritional improvement: case studies**

- **Proteins enrichment and fat reduction**
- **Sugars & energy reduction with maltitol**
- **Fibre enrichment with prebiotic fibres**

*Ms Carole Midon, Ms Virginia Millan, SYRAL Customer Technical Support*

A balanced diet is one that contains adequate amounts of nutrients and energy. Dietary Reference Values (DRVs) are used for planning and assessing adequate nutrient intakes: they are the complete set of nutrient recommendations and reference values, such as the average requirement, adequate intake level and the lower threshold intake and are also used for establishing food-based dietary guidelines (FBDG), which consist in specific food consumption recommendations based on nutritional recommendations.

At the EU level, EFSA has been asked by the European Commission to review the earlier recommendations for nutrients and energy of the Scientific Committee on Food (1992) and to help public authorities in Member States in translating nutrient based recommendations into practical food-based guidelines. This could change the current practice that still allows a food high in fat, salt and/or sugar to use claims such as "rich in vitamin C" or "high in fibre" to attract consumers, even if the overall health and nutritional benefits of the product are low. EFSA has first laid down the general principles for establishing dietary reference values, as well as the life stage, age and sex groups that will be considered in the setting of DRVs for energy and nutrients. EFSA expects to deliver the first part of its work related to energy and macronutrient, such as fats, proteins and carbohydrates, by 2009.

Consumers are more and more concerned on how their diet impacts the health and the body appearance: They want to eat more balanced food and to control their calorie intake all over the day. They not only want to fight obesity and to loose weight, but also to keep a healthy weight. This is far from being easy as we are often tempted to have a snack between meals such as a cereal bar or a cake. Moreover, most of the snacks are often high in fat, sugar and salt, and can leave you still hungry soon after eating. As consequence snacking can lead to inappropriate weight gain.

Hence the food industry is facing a difficult challenge to formulate foods which not only follow the new regulation and the coming nutrient profiles but also remain of good taste, are natural, of course safe and of a price not significantly different from the traditional foods. Fewer calories can be achieved in most foods by reducing the sugar and/or fat contents and by using digestible or non digestible (fibres) high molecular weight carbohydrates and polyols such as sorbitol and maltitol. Tools to answer to consumers concern on maintaining a healthy weight is - for instance - to offer alternative snacks which are lower in calories while ensuring to feel satisfied till a next regular and balanced meal: Relatively high protein foods diets have a positive impact on satiety by enhancing the feeling of fullness and increasing the delay of the next food.

Different formulations have been tested by the SYRAL Innovation team, all yielding high taste and nutritional quality products.

**High proteins cereals bars** (i.e. at least 20% of energy coming from protein as defined by the EU regulation 1924/2006) can be formulated by using Meripro - a soluble wheat protein. In this case, part of the glucose-fructose syrup and of the cereals blends were substituted by vegetable proteins. The texture more precisely the hardness and the tasting panel evaluations were not affected. Thus, products formulated with Meripro do not only promote satiety but can also enable to lower the sugar content compared to common snacks.

In a **cereal bars** recipe, the added sugars can also be totally replaced by Maltite® and Actilight® allowing claims on “**no added sugars**” as well as on “**fibre enrichment**” and “**prebiotic effect**”. As in the previous example, the tasting panel evaluation of the tested product is very good.

Isotonic drinks (i.e. drinks with an osmolality of 270 to 330mOsm/kg) have a similar carbohydrate electrolyte concentration to the body's own fluids: They are often preferred to water by athletes and are best used later in the recovery process to boost energy intake while still encouraging fluid uptake during the final stages of re-hydration. The use of proteins-carbohydrates solutions in the post exercise period may help to rapidly re-synthesis glycogen stores that were lost during the exercise. In a study focusing on **isotonic sport drinks**, more than 20% of calories can be provided by Meripro - a highly soluble wheat protein over the pH range, allowing claims on **proteins enrichment**. The tasting panel evaluated the high protein drink as acceptable even if it looks slightly more opaque than the reference.

**Smoothies** which can be described as blended, chilled, sweet beverage made from fresh fruits, juice or puree to create a drinkable texture, offer healthier treat than other snack options, taste good and also offer convenience and portability. The addition of Actilight® in a smoothie recipe allows claims on **fibre enrichment** and **prebiotic** effect. The flash pasteurisation (15 seconds at 72°C) after the homogenisation did not induce Sc-FOS hydrolysis. The tasting panel evaluation of the products does not show differences in sweetness, acidity, flavour and texture. The global evaluation of the product with Actilight® was even the best.

The challenge of producing good tasting products meeting the dietary guidelines has been met.

## **Afternoon session**

Nutrigenomics and obesity

Immunity and nutrition

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## **Metabolic syndrome and obesity: growing threats promoted by modern food habits**

*Dr. Jean-Michel Lecerf, Institut Pasteur Lille*

Metabolic syndrome (MS) is the most frequent polygenic metabolic syndrome in the world. Its prevalence is growing with the increase of obesity and inactivity. The most recognized definition is the 2001 ATPIII NCEP definition which must include 3 of the following criteria: waist circumference higher than 102 cm (male) 88 cm (female)-Fasting blood glucose higher than 110 mg/dl - Triglycerides higher than 150 mg/dl – HDL-C lower than 40 mg/dl (male), 50 mg/dl (female) - Blood pressure higher than 135/80 mmHg.

The main concern in the MS is the increase of visceral adipose tissue which is well correlated to waist circumference.

The visceral adipose tissue lead to a lot of abnormalities, through the production of free fatty acids which are directly provided to the liver, and induce hyperglycemia, hypertriglyceridemia and increase the cardiovascular risk and diabetes risk through insulin resistance and inflammation.

The increase of visceral adipose tissue is due to multiple factors: the occurrence of a thrifty genotype *in utero*, the stress through the hypothalamo-pituitary axis, and the way of life (dietary habits and physical activity). Many nutritional factors are associated to the metabolic syndrome, protective factors, consumption of whole grains, legumes, vegetables, fruits, dairy products... and negative factors: high glycemic index foods, and refined cereals, western industrialized foods, carbonated drinks and fructose.

Prevention of metabolic syndrome is based on physical activity and healthy diet. Treatment of metabolic syndrome needs a weight of loss with drug therapy, or improvement of diet balance and fight against inactivity. A diet with high fiber content, low glycemic index, omega 3 fatty acids and prebiotics in order to reduce insulin resistance and inflammation is useful.

## Studying modulation of gene expression by food diets: nutrigenomics applied to metabolic syndrome

*Dr. Jean-Charles Martin, Inserm, Marseille*

According to the International diabetes federation (IDF) definition, the metabolic syndrome (MS) is a cluster of the most dangerous heart attack risk factors: diabetes and prediabetes, abdominal obesity, high cholesterol and high blood pressure. A quarter of the world's adults have metabolic syndrome. The importance of this syndrome for human health and life expectation can be summarized by the following:

1. People with metabolic syndrome are twice as likely to die from, and three times as likely to have a heart attack or stroke compared with people without the syndrome
2. People with metabolic syndrome have a five-fold greater risk of developing type 2 diabetes
3. Up to 80% of the 200 million people with diabetes globally will die of cardiovascular disease

Nutrition is one of the important extrinsic factors that contribute to promote or to prevent the outcome of the MS. This can occur through the direct or indirect modulation of genes and gene products by macro or micronutrients. The study of nutrient-gene interactions is termed **Nutrigenomics**, examining how constituents of the diet interact with genes, and their products, to alter phenotype and, conversely, how genes and their products metabolize these constituents into nutrients, antinutrients, and bioactive compounds.

Bottom-up strategies, e.g. hypothesis driven research, targeting selected molecular pathways based on phenotypic observations, are often used to study the impact of nutrients on gene functions. Using this approach, it has been demonstrated that lipid components stand among the most powerful ones that can affect several aspects of the MS, through modulation of the anabolic/catabolic pathways, inflammation and metabolic stress. This occurs by interacting with nuclear transcription factors, which are protein regulating the activity of specific genes. Among lipid-sensitive transcription factors, PPAR's, SREBP1, HNF4A, LXRA play an outstanding role in controlling key metabolic pathways in various tissues, such as the liver, skeletal muscle and adipose tissues, and can be targeted by nutritional intervention strategy to improve MS outcomes.

Conversely, Top-down strategies, e.g. data driven hypothesis using wide system biology approach, become more and more popular to examine how nutrients can affect the multiple aspects of the metabolic syndrome. The information obtained can be used then to generate further hypothesis with regard to the mechanisms of action of nutrients toward MS, thus helping delineate the benefit-risk limit, or to unravel unexpected effect. This is the world of the 'omic' approaches, such as transcriptomics, proteomics and metabolomics now used in the context of nutrigenomics.

Some examples of recent studies using these disciplines in the perspective of nutrients-MS interactions will be given, thus emphasizing the importance of certain food components in the development of the MS: fatty acids, organic and mineral micronutrients...

Recent studies also indicate that the metagenome, e.g. the intestinal microflora, can be also affected by diet, and be implicated in the etiology of human disease. Dietary manipulations of the metagenome represent an interesting opportunity to improve the health status of individual, especially the MS.

## **Benefits of dietary fibres on metabolism regulation**

### **Example of short chain Fructo-Oligosaccharides**

*Ms Frédérique Respondek, SYRAL Scientific Affairs*

Type 2 diabetes, which is a consequence of overweight and associated metabolic alterations, has long been considered as a lifestyle disorder. Highest prevalence rates appear with “westernisation” and modernisation of countries and 70-80% of the cases are either associated with overweight or obesity. To control the global increase of obesity and its associated complications such as type 2 diabetes, nutritional management appears of great importance. Indeed, the balance between energy intake and expenditure, the type of carbohydrates and/or fat provided by the diet are important to take into account. According to a US study, lifestyle modifications including adapted diet and physical activity are even more efficient than drug treatment to reduce incidence of diabetes in the population.

Through their property to reduce glycaemic index of foods, benefits of dietary fibres has long been recognized by epidemiological studies. But the effects of several non viscous soluble fibres can not be explained by the reduction of glycaemic index and other mechanisms have to be proposed.

Using new techniques available to look into our digestive microflora composition and functionalities, researchers have pointed out the importance of colonic fermentations on weight regulation and on different metabolic pathways. Several situations linked to digestive microflora modifications whatever in level of fermentative activities or quality of these fermentations led to think that there is a link between colonic fermentation and insulin sensitivity. For example, it was shown that patients suffering from some inflammatory bowel diseases like Crohn’s disease or ulcerative colitis, which are know to be linked to modifications of the digestive flora composition in comparison to healthy people, also suffered from peripheral insulin resistance and decreased glucose tolerance.

Short-chain fructo-oligosaccharides (scFOS) are non viscous soluble fibres that are highly fermentable in the colon. In five out of seven clinical studies, dietary supplementation with  $\beta$ -fructans improved the HOMA-IR index, evaluated from fasting glycaemia and insulinaemia measurements. Trials with different animal models and different techniques of insulin sensitivity evaluation confirmed the benefits of scFOS to improve insulin sensitivity and help to explain them. Obese dogs receiving dietary supplementation of scFOS (given at around 4g/day) showed an improved peripheral insulin sensitivity and modified expression of several genes from subcutaneous adipose tissue, in comparison to when they received the control diet. Studies in rodent models will help us to define which modifications induced by scFOS at intestinal level may explain these positive outcomes evaluated at peripheral level.

## **Stimulation of immunity through nutrition**

*Dr. Philip Calder, University of Southampton*

The immune system protects the host from environmental infectious agents and other noxious insults. It also permits tolerance to self-antigens and to non-threatening environmental agents such as food proteins. The system has two functional divisions: the innate (or natural) immune system and the acquired (also termed specific or adaptive) immune system. The immune system cannot operate without an adequate supply of many different nutrients and both protein-energy malnutrition and individual micronutrient deficits cause significant compromise in immune defence, resulting in increased susceptibility to infection. Correction of general protein-energy malnutrition or of specific nutrient deficiencies can improve immunity and resistance to infectious disease. Amongst other dietary components, certain amino acids, fatty acids and prebiotics influence the function of the immune system. There is evidence that for some nutrients, intakes above those normally recommended or consumed can result in immune outcomes being enhanced above those previously seen. However whether this increases resistance to disease is not clear, with little convincing evidence at this stage. Not all immune responses respond the same way or to the same extent to increased supply of a given nutrient. Excessive intakes of some nutrients can impair the immune response.

## **The synbiotic approach from science to food formulation**

*Dr. R.A. Rastall, Department of Food Biosciences, University of Reading*

The use of probiotic micro-organisms to enhance and/or maintain gut health has a long history. Application of prebiotic carbohydrates to this end is much more recent, however. The combination of probiotics and prebiotics is the basis of the synbiotic approach. As the name suggests, the idea is to achieve a synergistic effect.

The scientific literature on synbiotics is not as well developed but there are increasing reports of synbiotics being used in a range of disease states. Notable among these are acute infections, inflammatory gastrointestinal diseases and colon cancer. Results have been mixed with some studies showing positive effects.

There is also interest in the food industry in the use of synbiotic formulations to improve the technological properties of probiotic bacteria. There is much less published on this aspect of synbiotic development and this is a fertile area of investigation for food technologists.

Generally, synbiotics studied to date have been formulated using commercially available prebiotics and probiotics. There is potential in the future, however, for the rational generation of synbiotic combinations to optimise specific effects. This process will be facilitated by the increasing sophistication of biotechnological approaches to the manufacture of functional carbohydrates. Further, increased understanding of the functional roles of bacteria in the gut, and of their interactions with their human (and animal) hosts will provide us with new targets for synbiotic intervention.

This presentation will evaluate the state of the art in synbiotic science today and present some of our recent findings on the biological activities of synbiotics.







