



ASSOCIATE PARLIAMENTARY FOOD & HEALTH FORUM



Inquiry into the links between diet, mental health and behaviour

10.30am-12.00pm, Thursday 25 October 2007

Jubilee Room, House of Commons

Introduction

Lord Rea welcomed members to the Forum's sixth inquiry meeting and thanked the guest speakers, Professor Alan Jackson, Director of the Southampton University Institute of Public Nutrition and Chairman of the Scientific Advisory Committee on Nutrition (SACN), and Dr Alan Dangour, a senior lecturer at the London School of Hygiene and Tropical Medicine, for agreeing to give evidence to the inquiry.

Professor Alan Jackson

Lord Rea introduced Alan Jackson, who is Professor of Human Nutrition at the University of Southampton. Alan became the Director of the University's Institute for Human Nutrition when it was established in 1995. He is Chair of the Government's Scientific Advisory Committee on Nutrition (SACN) which reports to the Food Standards Agency and the Department of Health on food and nutrition related issues. He was until recently a member of the European Food Safety Authority's Panel on Dietetic Products, Nutrition and Allergies.

Professor Jackson (AJ) explained that he was a paediatrician interested in human growth and development.

General advice to the population on fish consumption in the UK dates back to the work of the Committee on Medical Aspects of Food and Nutrition Policy (COMA)¹, which considered the nutritional aspects of cardiovascular disease. COMA recommended that people eat at least two portions of fish per week, of which one should be oily, in order to protect themselves against the risk of cardiovascular disease.

By 2001 the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) had become concerned that the contamination of fish with harmful toxins might represent a risk to consumers. They issued guidance on the possible harmful effects of eating fish as a result of environmental pollution and, in particular, the build up of dioxins and dioxin-like polychlorinated biphenyls (PCBs) in fatty tissues and hence oily fish. COT warned that dioxins and PCBs had the potential to cause damage to a developing foetus and identified them as a possible cause of cancer.

As a result of the COMA and COT guidance, from 2001 the public were receiving conflicting advice on the consumption of fish, so a joint committee of members of COT and SACN (which replaced COMA) was established to review the balance of risks and benefits of fish consumption. SACN's remit was risk assessment. It had no remit in risk management or risk communication. The joint committee was also asked to identify whether any sections of the population were particularly

¹ COMA, 1994, Nutrition Aspects of Cardiovascular Disease.

vulnerable to the risks associated with fish consumption. The joint committee was aware of the work of a Royal Commission on the Environment, which was considering the availability and sustainability of fish stocks.

The joint SACN/COT report was published in 2004² and captured advice up to that time. It used standard procedures for looking at and advising on the evidence. It consulted stakeholders during the review process to ensure that its work was transparent and in order to take into account current public concerns.

The SACN/COT report specifically addressed the balance of risks and benefits of fish consumption weighing the nutritional benefits of eating fish against the toxicological considerations. The joint committee identified various potential benefits of eating fish, particularly oily fish, because of its omega-3 fatty acid content. These included benefits associated with cardiovascular disease (secondary prevention, plaque stability, clotting, anti-inflammatory effects); pregnancy (duration and birth weight); neuro-cognitive development and function (where they distinguished between the effect on pre-term/full-term babies, infants, children and older people) and other benefits associated with blood pressure, obesity and arthritis. In their view the critical factor in terms of benefit from fish consumption is its DHA content,

As a result of the SACN/COT report, the Food Standards Agency (FSA) issued guidance in 2004 recommending an upper limit intake in terms of portions of fish per week as follows. There was no upper limit to the amount of white fish and canned fish that people could eat safely with the exception that pregnant women were advised to eat an upper limit of 4 cans of fish per week. Non-pregnant women and men were advised they could safely eat up to 4 portions of oily fish per week; girls up to the age of 16, pregnant women and lactating women were advised to eat up to two portions of oily fish per week. In all cases, one portion equated to 140g of fish or ~ 0.45 g/d long chain omega-3.

There are two critical factors associated with fish in terms of human nutrition. Cod liver oil is a rich source of vitamins A and D - and concern about inadequate intake of both vitamins in the UK has led to the mandatory fortification of yellow spreads (margarines) with vitamins A and D. Fish is also beneficial because it is a rich source of omega-3 fatty acids, which are known to prevent disease (such as heart disease) and promote health.

Fatty acids can be categorised as saturated fatty acids, mono-saturated fatty acids and poly-unsaturated fatty acids (PUFAs). Essential fatty acids, which include the PUFAs, have to be taken preformed in the diet because humans cannot create them from other foods. There are two families of essential fatty acids: omega-6 (linoleic acid) and omega-3 (linolenic acid). The body can synthesise PUFAs from these essential fatty acids. Arachidonic acid (AA) is derived from linoleic acid (omega-6) and EPA and DHA are derived from linolenic acid (omega-3)

Polyunsaturated fatty acids (PUFAs) are a critical structural component of all cell membranes. PUFAs also regulate cell function, acting as precursors for cell messaging.

Although humans can synthesise DHA from "parent" essential fatty acids, our ability to form adequate amounts of DHA by this means is unclear. The ability to synthesise DHA may be especially important during pregnancy, particularly for pregnant women who do not consume high amounts of DHA through their diet, such as vegetarians and vegans.

Pregnancy and the lactation period are also the time when the foetus/infant is most vulnerable to possible toxicants because it is a critical time for the growth and development of the brain.

Membranes of neurones in the brain require substantial amounts of omega-3 fatty acids, especially during development and of these omega-3 fatty acids, DHA is especially important. There is a greater proportion of DHA in retina tissue (some 60%) than in the brain (some 30%), but because

² Advice on fish consumption: benefits and risks, COT 2004.

the brain is much larger than the retina, the absolute amount of DHA required for the brain is greater.

The transition between late pregnancy and the first few months of infancy is a critical time for the development of the brain. The precise means by which a foetus obtains enough DHA for healthy brain development when its mother's intake is marginal remains a mystery.

Where maternal dietary supply of DHA is only marginally adequate and intake is not changed during pregnancy and lactation, meeting the increased requirement for DHA for the healthy development of the infant brain depends on conservation of long chain PUFAs by reduced oxidation; the amount of pre-formed EPA and DHA which can be accessed from adipose tissue reserves; and the ability to increase the formation of DHA from precursors such as linolenic acid (omega-3).

The ability to synthesise DHA in the liver depends on the availability of other micro-nutrients, including zinc, iron and magnesium and oestrogen status. If any of these are constrained, then the supply of DHA will be constrained unless it is consumed preformed in the diet. However, oestrogen levels are higher in women than in men and they are higher during pregnancy.

Breast milk contains generous amounts of DHA³ and, because of its importance for development, infant formula is now fortified with DHA for the sake of the baby's health.

Mental processing is significantly improved in babies with higher levels of DHA. When pre-term infants were studied, 9 out of 10 studies demonstrated improvements in visual function for those with higher DHA.⁴ When term infants were studied, the evidence was much less secure although 7 out of 11 studies found visual function was better in infants with higher levels of DHA.

There is also evidence that lower DHA levels are associated with a shorter gestation length⁵ and a greater risk of risk of preterm delivery.⁶

In response to a question from **Lord Rea**, Alan Jackson said randomised, controlled trials for term infants are more difficult because, for example, women who are more likely to breastfeed are likely to come from a different background to women who do not.

Behaviour development studies are difficult to undertake and they are more open to environmental factors. However, studies show that at the top end of development there is some effect.

Development needs to be put into context. When a baby is born the head is closer to full size than the baby's body. This suggests that the nutrients needed for the brain are more important at an early stage of development than at later stages. There is reasonable evidence that physical and intellectual development is needed before social development can take place. Thus, if an infant has an inadequate intake of nutrients needed at any particular stage of development, it is difficult to make up for this lack of nutrients at a later stage.

The Countess of Mar asked whether the Government had been right during World War II to give pregnant women cod liver oil and whether this policy should be repeated. **Alan Jackson** said it had been right during the war because of concern about inadequate intakes of vitamins A and D. Now, the authorities are concerned that pregnant women may eat excessive amounts of vitamin A, so they are advised to supplement with vitamin D, but not vitamin A. **Lord Rea** asked if some of the benefit of cod liver oil was due to its omega-3 content. Alan Jackson said omega-3 was present in cod liver oil, but in relatively small amounts.

³ Makrides 1994

⁴ Williams 2001; Jorgensen ~ 2001

⁵ Olsen ~1992 & 2000; Smuts ~ 2003

⁶ Olsen & Secher 2000

Ian Gibson asked Alan Jackson to comment on the evolutionary aspect of man's consumption of fish. **Alan Jackson** agreed that man has probably always eaten fish, but the critical factor is how good we are at synthesising DHA from EPA. Vegetarians and vegans are likely to take in their diet all the other micronutrients they need to facilitate the synthesis of DHA from EPA.

For normal development children need challenges in play and the nutrients necessary to enable them to respond to those challenges. If they do not have adequate nutrients it could affect their long term development. Issues concerning behaviour in later childhood and adolescence relate to early development and there is not enough evidence on this yet. This is a relatively new field and it is very complex. It is difficult to model in a way that will give us a secure understanding of the issues. The sort of trials necessary (randomised, controlled trials) are very expensive and they need to take place over a long period of time. They cannot be organised by individual scientists, but require a systematic approach. However, we do not have a mechanism for setting up this sort of work: it is not possible for young scientists to develop a career in this way because the results will not be available for many years. We do have large trials looking at large populations over time when genetic risks are being evaluated, but it is much harder to obtain funding for nutritional risks.

Lord Rea asked if there is sufficient evidence to press for funding for trials assessing nutritional risks. **Alan Jackson** said he and colleagues who were interested in nutrition for women before and after pregnancy could only afford to carry out their work in India because of the high costs of running such a trial in the UK. The Southampton Women's Study had been very difficult to resource and it does not have secure funding.

Alan Jackson emphasised that it is possible to see a major role for many nutrients in terms of brain function. Glucose, for example, is vital for brain function. Lipids are necessary for the brain structure and communication. Amino acids (proteins) are necessary for communication and affect mood. Each nutrient inter-relates with others. For any to work they require a wide range of micronutrients. One nutrient should not be singled out from the others. The body's ability to support the brain is, more than anything, a function of the inter-related work of a wide range of nutrients. We also have a long way to go in ensuring people eat a varied, healthy diet. SACN recommended pregnant women should eat up to two portions of oily fish a week, but average consumption is one-third of a portion a week, so we remain far from reaching sensible levels at the present time.

Questions

Ian Gibson asked if any country had achieved the optimum level of fish consumption. **Alan Jackson** thought not in the deliberative sense implied by the question.

Earl Baldwin of Bewdley referred to recommendations produced by VKM, the Norwegian Scientific Committee for Food Safety (English translation published in 2007) which said "it is the opinion of VKM that there is no risk associated with eating fish and other seafood in amounts equivalent to four meals or more per week as long as different fish species are eaten and the consumption of fatty fish, with the current levels of dioxins and dioxin-like PCBs, does not exceed two meals per week." He asked Alan Jackson to comment on it. **Alan Jackson** had not seen the Norwegian recommendations but said that the VKM had a very good reputation. He added that the number of recommended portions would reflect the safety margins chosen and these are crude estimates and could be changed.

Ian Gibson asked whether changes in behaviour, such as the increasing incidence of anti-social behaviour, could be attributed to poor diet. **Alan Jackson** said it is very difficult to know with security how diet and behaviour are related. Fish and omega-3 has to be seen as part of a good quality diet. SACN is about to produce a review of National Diet and Nutrition Surveys (NDNSs) since 1997. Even the most optimistic person would have to say there are some aspects of the British diet that are worryingly bad, especially among teenagers and young people in their twenties. There is reasonable data in the global literature which shows that factors that influence the development of the brain can be related to the quality of social behaviour in an important way. It is not easy data to put together, but it deserves serious and careful consideration.

Lord Rea asked if there was any evidence that the level of toxins in fish is falling as a result of improving environmental standards. **Alan Jackson** said that dioxins and PCBs last a very long time, so we would need to look for changes over a long period. Local concentrations depend on local activity and these are monitored.

The Countess of Mar observed that pregnant women can take in dioxins through food other than fish, such as dairy products. **Lord Rea** asked what other food items are likely to be significant sources of dioxins. **Alan Jackson** said dioxins and PCBs are present in all natural food, but they are concentrated in fatty tissue, hence they are a particular risk in oily fish.

Mr Alex Smith of Alara Wholefoods noted that Alan Jackson had suggested that foetal DHA levels were attributed to maternal synthesis of DHA from EPA and asked what ability the foetus itself has to synthesise DHA. **Alan Jackson** said he was not aware of any evidence on this issue, but he would be surprised if the foetal liver could synthesise DHA in the quantity required.

Professor Jack Winkler referred to the SACN/COT report recommendation, which described up to two portions of fish a week as a “minimum and achievable target”, not an optimum level and asked what evidence there was that this was “achievable”. **Alan Jackson** said SACN/COT were operating between what was regarded as inadequate levels and dangerously high levels of fish consumption. They were trying to encourage people to reach the levels of fish consumption that had been recommended by COMA in 1994. There is evidence that a higher level could be beneficial for health in terms of reducing the risk of cardiovascular disease. One portion a day does not necessarily achieve the best physiological function, but the dose-response curve for this is not clear. There is no evidence that four portions of fish a week will confer harm in terms of essential fatty acids; the concern relates to toxins.

Dr Beckie Lang of MRC Human Nutrition Research noted that fatty acid supplements vary greatly and asked if there is a minimum dose of EPA and DHA that is beneficial. **Alan Jackson** said it was not appropriate for him to comment on this issue, which went beyond his remit.

Lord Rea asked Alan Jackson to single out the nutrient that we were most at risk of consuming inadequately as a result of the modern diet. **Alan Jackson** said that the SACN review of NDNSs suggested that we should be most concerned about inadequate intakes of micro-nutrients, including B12, riboflavin, selenium and vitamins A and D. The advice of Government to eat a varied, healthy diet really is important: we need a better range of nutrients than we currently eat.

Professor Jack Winkler asked Alan Jackson to comment on the ALSPAC study (Lancet, February 2007), which had concluded that the present levels of fish consumption for pregnant women recommended by the FSA was sub-optimal. **Alan Jackson** said it was one study among a number and he had no comment on it.

Dr Alan Dangour

Lord Rea introduced Dr Alan Dangour, who is a senior lecturer at the London School of Hygiene and Tropical Medicine. Alan’s research focus is nutrition in older age, and he is conducting a series of trials to determine the effectiveness of nutrition interventions for the maintenance of health and function in later life. Alan is the principal investigator of the [OPAL study](#) which is a randomised controlled trial designed to determine the effect of daily supplementation with omega-3 long-chain polyunsaturated fatty acids on cognitive and retinal function in older people in the UK.

Alan Dangour said he intended to focus on the strength of the evidence relating to essential fatty acids and to look at both children and older people.

Alan showed a slide (slide 3), which described the strength of evidence pyramid, which ranges from animal research and in vitro studies at the bottom, to systematic reviews and meta-analysis at

the peak. Systematic reviews are extremely powerful tools for analysing all the published material on a subject to achieve strong statistical evidence.

There is a clear need for essential fatty acids, especially DHA, for the healthy development of the brain. The brain is 22-24% lipid, with high concentrations of omega-3 long chain poly-unsaturated fatty acids (n-3 LCs), especially DHA, in brain and retinal phospholipids. There is a clear need for DHA *in utero* (and during the first 2 years of an infant's life) for optimal brain and retinal development. DHA effects gene expression, neurogenesis, membrane structure and function, protein lipid interactions and receptor binding. Very new data⁷ suggests DHA has an effect on the release of neurotransmitters, which may have potential impact on the mood/behaviour of children.

We are aware of some potential mechanisms for links between essential fatty acids (EFAs) and behaviour. However, the University of Teesside review of diet and behaviour for the FSA, which looked at five trials studying EFAs and childhood performance, concluded that the findings of these trials were mixed and therefore inconclusive. Only the Oxford-Durham trial reported consistent improvements in both objective and subjective behavioural and educational outcomes. Moreover, caution is required when translating the evidence of effect from children with neurodevelopmental disorders to mainstream school children. It should also be noted that the dosages in supplements used in the trials are unlikely to be achieved through diet alone. However this is an issue of public health importance and further large scale trials in this area are needed.

The results of the Nutrition Enhancement for Mental Optimisation (NEMO) Study Group have recently been published in the American Journal of Clinical Nutrition (2007). The study included 396 well-nourished children aged 6-10 in Australia and 384 marginally nourished children in Indonesia. This randomised controlled trial was testing the effect of multi-nutrients (iron, zinc, folate, and vitamins A, B₆, B₁₂, and C), fish oil (110mg/d), both or neither for 12 months on learning and memory. They found that the blood nutrient profiles improved over 12 months; that fish oil had no effect on learning outcomes; and that multi-nutrients had a small effect on learning and memory, but no effect on intelligence and attention. Contrary to the expectations of the researchers, the small effect of the multi-nutrients was noted in the well-nourished children in Australia, not the marginally nourished children in Indonesia.

A summary of the data on EFAs and children indicates that there are some potential mechanisms of effect. The evidence of effect of EFAs on ability and behaviour among school-age children from randomised controlled trials (RCTs) is inconclusive. Most of the RCTs have been small, relatively short and mostly limited to children with neurodevelopmental disorders. However, this is an issue of importance for public health and large RCTs in this area are urgently needed.

Earl Baldwin asked how much it mattered that the RCTs had focussed on children with neurodevelopment disorders. **Alan Dangour** said it would clearly be good if we could find a way to help these children - and there may be some evidence of benefit for these children – but it is important to clarify that the evidence does not apply to healthy children.

There are now 24.3 million people with dementia and 4.6 million new cases every year. By 2040 it is estimated there will be 81.1 million people with dementia, which will reflect a 100% increase in developed countries and a 300% increase in India and China as a result of ageing populations. Many more people are now living longer and thus reaching the age at which dementia typically occurs. In UK today there are 700,000 cases – 1 in every 88 people – this is expected to rise to 940,000 cases by 2021 – 1 in every 71 people – and to 1,735,000 by 2051.

There are some very interesting studies in the US looking at microthrombotic obstructions in the brain as a cause of dementia.

We have a very good idea of why n-3 long-chain polyunsaturated fatty acids may be beneficial for the ageing brain. DHA is metabolised to *neuroprotectin D1*. DHA regulates gene expression.

⁷ Innis S. 2007

Combined with EPA, actions may: improve vascular integrity, reduce microthrombotic obstruction and enhance neuronal health and signalling.

Several important studies have looked at the role of diet for cognitive health. One of the earliest by Goodwin⁸ was a cross-sectional study of 260 community living adults aged 60+ years. He found that low blood levels of vitamin C and B₁₂ were associated with worse cognitive function.

Numerous surveys show associations between nutrients and cognitive function, but caution is needed when looking at cohort study results. RCTs are needed to tease out the cause and effect and to isolate the relevant factors.

A systematic review of the evidence on fish oils and cognitive function was conducted by Issa.⁹ It limited the studies it considered to those dealing with humans; RCTs, cohort or case-controlled; and those describing the effect of fish oil on cognitive function, or incidence/treatment of dementia. Of 5,865 citations, they found only 5 relevant studies (4 cohort studies, 1 RCT). The review concluded that in the four [cohort] studies that assessed the effects of n-3 LCPs on incidence and treatment of dementia, a trend in favour of n-3 LCPs (fish and total n-3 consumption) toward reducing risk of dementia and improving cognitive function was reported. The one RCT included in the review was small and of poor quality.

An example of the cohort studies included in the systematic review presented information on fish consumption and risk of dementia.¹⁰ This study looked at 1674 free-living French people aged ≥ 68 years over a follow-up period of 7 years. It found that those with the highest fish consumption had the lowest risk of incident dementia over the follow-up period.

A Cochrane Review in 2006 could not identify a single RCT in this area. It concluded: "There is a growing body of evidence from biological, observational and epidemiological studies that suggests a protective effect of n-3 LCPs against dementia. However, until data from randomised trials become available for analysis, there is no good evidence to support the use of dietary or supplemental n-3 LCPs for the prevention of cognitive impairment or dementia."

An RCT¹¹ of 174 people aged 74 years with Alzheimer's disease and Mini Mental State Examination (MMSE) scores of greater than 15 (30 is maximum) showed no evidence of benefit for either 1.7g DHA + 0.6g EPA or placebo. However, in further analyses looking only at individuals with MMSE >27, n-3 LCP supplementation appeared to slow the decline in MMSE score over 6 months.

Another recently completed RCT (MEMO) included 302 healthy older people aged 65+ years in Holland with a MMSE score of >21. Study participants were randomised to placebo, low-dose or high-dose n-3 LCPs for 6 months. This study (van der Rest) has been submitted for publication and the results are not yet available.

People often ask why, when cohort studies demonstrate an effect, it is not replicated when RCTs are carried out. There are numerous possible reasons. It may be because of residual confounding (eg cohort studies may not be able to adjust for all potential environmental influences); it may be because the trials are too short or too small; the supplement dose may be too low; the outcome measures may be inadequately sensitive; the baseline status of the subject may vary; and the genetic status of the subjects may vary.

A summary of the data on EFAs and mental health in older people is that there is good mechanistic evidence of potential effect; some evidence from surveys; good evidence from cohort studies; no

⁸ Goodwin, JAMA, 1983

⁹ Dement Geriatr Cogn Disord, 2006

¹⁰ Barberger-Gateau, BMJ, 2002

¹¹ Freund-Levi, Arch Neurol, 2006

evidence of effect from RCTs and large RCTs are urgently needed. The Older People and n-3 long-chain polyunsaturated fatty acid (OPAL) Study is one such large RCT.

The OPAL study (funded by the UK Food Standards Agency) is testing the hypothesis that daily supplementation for 24 months with 0.7g of omega-3 LCPs (0.5g DHA + 0.2g EPA) - the equivalent of two portions of oily fish a week - will slow cognitive decline in older people. It is also testing the hypothesis that daily supplementation for 24 months with 0.7g omega-3 LCPs will benefit eye health in older people. The OPAL study is a double-blind placebo-controlled RCT. The people being tested are 868 cognitively healthy adults aged 70-79y drawn from 20 GP practices in UK. They are provided with capsules for daily consumption over 24 months. Cognitive function tests are being taken at 0 and 24 months and retinal function tests are being taken by a sub-sample of the group. The results are due in autumn 2008. More detailed information about the trial is available at: www.opal-study.org.uk.

Alan Dangour summarised his views by suggesting there is currently no good quality evidence from RCTs to support the use of fish oil supplements to enhance academic or behavioural performance in school-age children. There is currently no good quality evidence from RCTs to support the use of fish oil supplements to slow or prevent cognitive decline in older people.

Questions

Alan Dangour was asked how cognitive function is tested in the OPAL study. He said that they were using a battery of well-validated cognitive tests such as the Californian Verbal Learning Test, which are commonly used in studies among older people. He also explained that retinal function tests were only being done on a sub-sample (56/868) of the total group for reasons of cost and accessibility to Moorfields Eye Hospital where the retinal tests are being undertaken.

Professor Jack Winkler asked if the OPAL study measured baseline status and genetic make-up. **Alan Dangour** confirmed baseline nutritional and genetic evidence had been taken. He said that it is possible that n-3 LCP supplementation may benefit some genetic types more than others, but the likelihood is that such people will be equally split between the active and control group.

Conclusion

Lord Rea thanked both speakers for their presentations and brought the meeting to an end.

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