

A consensus review of the MAFF Lipids Programme: objectives and key achievements

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Introduction

In April 1999, we were awarded a 12-month contract by the Joint Food Safety and Standards Group in the Ministry of Agriculture, Fisheries and Food (MAFF) to review the MAFF Lipids Programme which had been in existence since 1992. We had three main objectives:

(1) Familiarisation with MAFF research on lipids. Construction of survey to contractors in MAFF Lipids Programme to evaluate published and unpublished results from research and to provide an audit of stored samples, etc. Administration of survey and evaluation of responses using electronic means of communication wherever possible.

(2) Evaluation of results from MAFF Lipids Programme 1992–99, with special emphasis on results obtained since 1996. Evaluation of results from similar programmes, over a similar timescale.

(3) Organisation of a workshop of UK experts to discuss the main themes of the Programme in relation to emerging 'hot topics' in the area of lipids and MAFF. Organisation of second workshop to address similar topics, but to involve international experts. Conclusions and future research identified, along with possible collaborations for EU Fifth Framework Programme. Consensus forming techniques to be used throughout. Consultation with experts on conclusions from evaluations and workshops; consolidation of findings into a Consensus Document which will translate the scientific discourse into the context of future decision and policy making in time for consideration by the Food Standards Agency and the next formal Review of the Lipids Programme.

Key achievements related to objectives

Objective 1

A questionnaire was constructed and used to assess the views of all 27 contractors within the MAFF Lipids Programme (representing 35 projects or joint projects) on three different aspects of the programme, namely;

- The MAFF Lipids Programme in general (proposal process, monitoring, workshops, collaboration)
- Scientific factors relating to their own project (e.g. area of study, problems encountered)
- Added value arising from the projects (e.g. new methods, or samples in storage).

There was general approval for the overall management of the MAFF Lipids Programme. Suggestions for improving the commissioning process included the establishment of a wider consensus on research needs prior to commissioning research and the screening of short submissions prior to inviting full proposals. More than 50% of projects involved collaboration with other MAFF contractors, mostly on the initiative of the proposers themselves, but there was a need for the promotion of multicentre collaborative studies to improve statistical power (and maximise expertise). Workshops were highly rated by contractors, although these could be more focussed and interactive and involve contractors more in the planning.

The MAFF Lipids Programme has resulted in the publication of around 60 full scientific papers, with a similar number in preparation, and in more than 100 abstracts. More than half of completed projects were rated (by the contractors themselves) as very/totally successful, one third as moderately successful and less than one in 10 as not very or not at all successful. Most of the changes that would be made with the benefit of hindsight related to techniques/equipment/sample materials used, the remainder to statistical design or choice of subject group. Studies that did not achieve their

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objectives may still be valuable, and around half the projects in the programme resulted in the generation of new hypotheses.

More than 80% of studies involved the collection of biological samples. In each case, around half remain potentially available for future investigations.

Objective 2

MAFF, as the department of Government with lead responsibility for food and the national diet, has the remit to investigate the role of particular foods and the diet as a whole, so far as they may affect biological processes which in turn can influence health and the risk of disease. The MAFF Dietary Lipids Research Programme had been set up in 1992 after the MAFF/Department of Health Inter-Departmental Liaison Group had identified the link between dietary fat and cardiovascular disease (CVD) as a high research priority. The major policy objective of the MAFF Dietary Lipids Research Programme (ANO2) was therefore to provide a robust basis for population level guidelines on achievable and palatable changes to the dietary lipid composition in the UK as part of the strategy to reduce CVD rates as proposed in the *The Health of the Nation* (Department of Health 1992). With the publication of the Coronary Review Group (CRG) Report in 1994 (Department of Health 1994) the scientific objectives of MAFF Dietary Lipids Research Programme became more focussed on addressing some of the research recommendations from this committee. With time they have evolved to cover other areas of relevance relating to the topic of dietary lipids and CVD that would now have to be taken into consideration when assessing dietary requirements for lipids.

CRG made recommendations for research; eight of these were for research into the 'diverse biological effects of dietary lipids.'

- (1) We recommend that research is continued and enhanced into the biological effects of different saturated fatty acids, and into practical ways in which such knowledge might improve public health.
- (2) The effect of dietary stearic acid on platelet function should be studied.
- (3) Further research is required on the effects on the serum cholesterol response to particular saturated fatty acids or their position in the triglyceride structure and of LDL receptor activity.
- (4) The effect of dietary fat and fatty acids on the tendency to thrombosis deserves further research.
- (5) The effects of *n*-3 fatty acids on platelet function require further research.

(6) The long-term consequences of average intakes by the population of *n*-6 polyunsaturated fatty acids in excess of about 6% of energy and individual intakes in excess of about 10% of energy should be studied.

(7) The possibility that dietary cholesterol may influence CHD risk by a mechanism other than through plasma cholesterol requires further investigation.

(8) The effects of interactions between dietary cholesterol and fat intakes on cardiovascular risk need further investigation.

Four of the CRG research recommendations (1, 3, 4, 6) have been covered in some way by the MAFF Lipids Programme (Category 1). These are reviewed fully in our report to MAFF to place the MAFF-funded work in the wider context of all other major research in this field (Ashwell *et al.* 2000). Eight further topics, not specifically identified in the CRG report, have also been covered in the Programme. Five of these (Category 2), where there has already been substantial MAFF input, are also reviewed fully in our report to MAFF to place the MAFF-funded work in the wider context of all other major research in this field. Subsequent papers in the *Nutrition Bulletin* will detail the findings within Categories 1 and 2.

The remaining three topics (Category 3), where MAFF-funded work has only just started, have not been covered in this way. The four recommendations from the CRG Report which were not covered in the MAFF Lipids Programme were discussed at the Workshops and conclusions about the advisability of tackling these issues now were agreed (see Objective 3).

The MAFF research areas, categorised as explained above, are:

Category 1

- Dietary lipids and lipoprotein metabolism
- *Trans* fatty acids effects on thrombosis, fibrinolysis and formation of atherosclerotic lesions
- Dietary fat intake, role of lipid peroxidation and antioxidant nutrients (intake, absorption, effect)
- Relative effects of individual fatty acids (especially oleic, *n*-6 and *n*-3 fatty acids) on haemostasis, vasomotor tone, nitric oxide metabolism and endothelin
- Effects of triacylglycerol structure on metabolism, transport and tissue uptake in man.

Category 2

- Effects of dietary lipids on insulin sensitivity
- Dietary lipids and immune function

- Relationship between dietary fatty acids and composition of atheromatous lesions
- Conversion of alpha-linolenic to long chain polyunsaturated fatty acids (PUFAs), effects of diet and importance in terms of CVD risk factors; *in vivo* oxidative stability of alpha-linolenic acid compared with long-chain PUFAs.
- Interaction of fatty acids with apoB and ACE polymorphisms.

Category 3

- Influence of fatty acids on apo A and Lp(a)
- Optimal levels of different fatty acids in the diet
- Diet effects on CVD risk in ethnic groups and targeting of dietary advice.

Objective 3

Two successful workshops were held and 12 different issues relating to the MAFF Lipids Programme were discussed. The workshops involved all MAFF contractors, MAFF officials and other selected experts in the field of Lipids and Cardiovascular Disease. A consensus was reached on each issue and these 12 clear recommendations were made to MAFF.

(1) A clearly communicated MAFF strategy for lipid research is needed. An 'overarching' advisory committee to select issues (and commission prior reviews) could be set up. Options for a 'free range' category in research and a two-tier (short-term and long-term) system for commissioning research should be investigated.

(2) Collaboration, or larger groups with adequate clinical and analytical facilities for longer/larger studies, are clearly desirable but must be set up with an integrated strategy which MAFF is well placed to initiate. Hypotheses must be fully developed and good pilot dietary intervention studies are essential for the successful design of large studies.

(3) MAFF should start by considering how its research can dovetail into the EU funded research in this area which must, by necessity, involve more than three countries. Some EU projects are already receiving 'top-up' funds from MAFF, so MAFF must ensure that it benefits from the results of the total EU research project.

(4) The current MAFF programme has covered the importance of triacylglycerol structure on CVD risk but not produced conclusive results. MAFF needs to revisit the previous five MAFF projects on the importance of triacylglycerol structure and then set up a dedicated centre to make triacylglycerols by new technologies before embarking on any further research in this area.

Liaison with industry is a worthwhile direction to pursue.

(5) MAFF funded research on dietary saturated fatty acids has shown them not to be more detrimental than other fatty acids with respect to haemostasis, insulin sensitivity or cytokine production. More work is still needed on saturated fatty acids with emphasis on long-term studies, individual variation in response and the interaction of saturated fatty acids with other components of diet.

(6) The MAFF funded research on *cis* monounsaturated fatty acids (MUFAs) and *trans* MUFAs has been fairly substantial and has demonstrated that current dietary recommendations for MUFAs are optimal. Further work is still required on MUFAs. In particular, the long-term effects of using MUFAs, rather than carbohydrate, to substitute for saturated fatty acids in the diet and the effects of different types of MUFAs on newly emerging risk factors such as postprandial lipaemia. Research on *trans* fatty acids should concentrate on determining the upper limits of safe intakes for different population groups.

(7) The MAFF funded research on *n*-3 and *n*-6 polyunsaturated fatty acids (PUFAs) has been fairly substantial and has demonstrated some beneficial effects of fish oils on cardiovascular risk. However it has also demonstrated problems with high intakes of both *n*-3 and *n*-6 PUFAs. Further work should concentrate on the effects of *n*-3 PUFAs in primary and secondary prevention trials with particular emphasis on the role of alpha linolenic acid and long chain *n*-3 PUFAs and the role of fish oils and the other components of fish. The possible adverse effects of both *n*-6 and *n*-3 PUFAs still need further investigation.

(8) The current MAFF Programme puts no priority on research on fish oils and platelet behaviour. Platelet behaviour is not an easy function to measure. MAFF should review research and achievements/gaps/problems, decide on hypotheses and methods, and only then decide on further research topics.

(9) There has been limited MAFF-funded research on the effect of stearic acid on platelet function and coagulant activity. The recommendation of COMA that further research be conducted on long chain saturated fatty acids, especially stearic acid, with respect to platelet function and coagulant activity does not deserve further attention as such, but the general issue of the effects of different saturated fatty acids on several areas of metabolism still needs addressing.

(10) There has been limited MAFF-funded research on the effects of different saturated fatty acids (c12 to c16) on LDL cholesterol levels and activity. Further work

should be done in this area, but it needs to reflect the current thinking about mechanisms such as the function of immune cells and vascular endothelium within the atherogenic process. Care should be taken to study the effects of saturated fatty acids within triacylglycerol, and to be more specific in the study of the effects of the saturated fatty acids on the composition of low density lipoprotein (LDL), as well as the size of the LDL particles in determining atherogenicity. The interactions between saturated fatty acids and dietary cholesterol need further study and the effect of saturated fatty acids in subjects showing different stages of the disease process. MAFF's general rule about only funding studies on normal healthy individuals might need to be reconsidered.

(11) MAFF's Lipid Programme has paid little attention to total fat intake and its relationship to CVD. There are many important questions to be answered such as the relationship of lipids and obesity, but the important lesson to learn is that the effects of dietary lipids extend beyond CVD and that these effects must not be forgotten. In the 1996 review, the MAFF Lipids Programme was criticised for being too wide-ranging and it was then focussed on dietary lipids and CVD. This recommendation should stand, but attempts should be made to liaise with other funding bodies to maximise the results from the MAFF Lipids Programme. Issues of compliance to lower fat intakes and meal patterns could be covered in other MAFF research programmes, such as AN09.

(12) There is great potential for an 'added value scheme' from the MAFF Programme on lipids. MAFF should commission a feasibility study to investigate certain aspects (costs/ethics/practicalities) of setting up a resource base/storage depot. Staff, volunteers, samples, data and equipment should all be considered in this study. MAFF should then set up a project to test the scheme/process prospectively.

Overall Conclusions

The whole subject of the role of reduced or modified fat intake for the prevention of cardiovascular disease has just been systematically reviewed by the Cochrane Centre (Harper *et al.* 2000). This review of 27 randomised controlled trials with 40 intervention arms and 30 901 person-years of observation, concludes that there is 'a small but potentially important reduction in cardiovascular risk in trials of longer than two years duration. Dietary advice to those at high risk of cardiovascular disease (especially where the statin drug group are unavailable or rationed) and to lower risk in

population groups, should continue to include permanent dietary fat modification. It was not clear whether a low fat diet, a modified fat diet or a combination of both is most protective of cardiovascular events'.

The nature of MAFF funding has meant that, rather than fund long-term trials, MAFF has had to focus on the mechanisms by which dietary lipids can affect markers of cardiovascular disease. This decision has now been vindicated by the Cochrane conclusion since trials shorter than two years would have been a waste of money. It is also encouraging that such a thorough review of the 'gold standard' intervention trial should have concluded that there is a definite role for dietary lipids in the prevention of CVD. The next question is 'how is this protection achieved?' Fortunately, the MAFF programme has already gone some way to answering this question.

The overriding conclusions about the MAFF-funded work are that these projects have contributed substantially to the research field in general and that they have definitely benefited from all being placed within a strategic, co-ordinated, programme. The topics identified by the CRG report which have not been covered by the MAFF Lipids Programme, such as platelet function and interactions between dietary cholesterol and fat intakes, have proved to be of less importance than the newer topics, such as insulin sensitivity and immune function. Decisions made to set research requirements for the Programme in relation to the emerging science rather than to follow rigidly all the recommendations in the 1994 CRG Report have also been vindicated.

We hope that the conclusions from our review can form the basis of an ongoing programme of work on the role of dietary lipids in cardiovascular disease as part of the policy objectives of the new Food Standards Agency. There is no doubt that the continuation of such a programme is justified.

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