Dr P Miller,
GACS Secretary
Room 3B, Aviation House
125 Kingsway
London WC2B 6NH

by email to: Patrick.Miller@foodstandards.gsi.gov.uk

5th October 2010

Dear Dr. Miller,

Re.: Second letter from GACS Review Sub-Group on the Agency-funded systematic review of nutrient content of organic and non-organic foods

Many thanks for your letter dated 17th September in which you acknowledged receipt of our letter of 10th September and thanked us for our response. We are grateful for this opportunity to respond to a further set of points raised by the Soil Association, the Organic Trade Board and the GACS Sub-Group.

As before, the attached responses reflect the combined views of Professor Ricardo Uauy, Dr. Elizabeth Allen and Dr. Alan Dangour from the London School of Hygiene & Tropical Medicine (LSHTM) Review Team. Dr. Karen Lock, the other senior member of the LSHTM Review Team remains on maternity leave. The responses have again been reviewed and approved by Professors Julie Lovegrove and Martin Wiseman from the Independent Expert Review Panel.

We have responded to the three primary points highlighted in the second letter from the GACS Sub-Group. We would again like to reaffirm that the scientific content of our work underwent multiple peer-review, first at the Food Standards Agency (both internal and external review) and then again before publication in the American Journal of Clinical Nutrition.

Yours sincerely,

Dr. Alan Dangour
Senior Lecturer
Response

Point 1

Firstly, the Soil Association response, which included commentary from Kirsten Brandt at Newcastle University, identified 28 papers which it suggests should have been included in the analysis (see attached list). The Sub-Group would welcome your comments on the reasons for exclusion of these papers. I note that several of these are included in the summary of ‘excluded papers’ published as part of the supplementary information with the web version of the first AJCN paper; in these cases please feel free to add to the brief commentary provided there.

1. On 7th December 2007, a team from LSHTM (lead researcher Alan Dangour) tendered for a contract from the Food Standards Agency which required an “independent systematic review of all scientific literature which identifies and assesses all published research studies that assess the nutrient and non nutrient content comparing organic and conventional food”.

2. The Agency specification for the review was (verbatim from requirement document):
   i. identify and evaluate all relevant studies aimed at comparing the nutrient (e.g. protein, fats, carbohydrates, fatty acids such as omega 3s, vitamins, minerals etc) and non-nutrient (including secondary metabolites, plant sterols, flavonoids, anti-oxidants, lycopene etc.) content of organic and non-organic food;
   ii. assess the studies strengths and weaknesses, and that the studies’ conclusions are sound and whether the studies make valid comparisons of organic and conventional food;
   iii. carry out a comprehensive systematic review of the body of evidence as a whole, identifying whether and where any nutrient and non-nutrient compositional differences occur;
   iv. assess whether any proven nutrient or non-nutrient compositional differences have any nutritional or other health significance in the context of the overall diet.

3. In our tender document, we interpreted the Agency specification as follows:
   i. conduct a systematic search process to identify all relevant published literature evaluating the central research question “Is there a difference in the composition of nutrients (and other nutritionally-relevant substances) of organically and conventionally produced foodstuffs?”;
   ii. grade the quality of the identified relevant publications;
   iii. conduct meta-analysis of data from relevant publications to identify whether there is statistically significant evidence of differences in nutritional composition between organically and conventionally produced foodstuffs;
   iv. state the relevance to health of any compositional difference(s) identified. With regard to this final point we note that in our systematic review on nutrient content we interpreted any statistically significant differences in the light of a normal healthy diet (see Point F in letter to GACS Sub-Group dated 10th September 2010). To rigorously interrogate the strength of available published evidence on the nutritionally-related health benefits of consumption of organic foods we conducted a second systematic review (Dangour et al. 2010 attached).

4. In late 2007, we were awarded a contract from the Agency (PAU221) to conduct the required work. We made our peer-reviewed protocols available online on 18th April 2008, we published our reviews as reports on the FSA website on 29th July 2009, and as two separate papers in the American Journal of Clinical Nutrition (AJCN) on 29th July 2009 and 12th May 2010. All extracted data used in the analysis published in the AJCN on the nutritional composition of foods was made available on the AJCN website after publication, and the full dataset from all identified studies was made available on the 25th May 2010 on the FSA website.
5. Given the specific nature of the Agency research requirements, studies included in the systematic review were required to report a direct comparison of the content of a nutrient (or other nutritionally relevant substance) in organically and conventionally produced foodstuffs.

6. We conducted a systematic search of the three most important scientific databases (PubMed, Web of Science, and CAB Abstracts), hand-searched the reference lists of relevant articles and contacted 40 subject experts to identify all relevant publications (see Point A in letter to GACS Sub-Group dated 10th September 2010). Despite these efforts, we acknowledge that we may not have identified all relevant publications and we note that this is a generally accepted limitation of all systematic reviews.

7. Of the 28 papers on the list provided by the Soil Association and the Organic Trade Board, we identified 24 in our systematic review process, and all 24 of these papers were excluded from the analysis. One of these papers (Mogren 2008) was excluded at Step 1 of the study selection process (see Figure 1 of Dangour et al. AJCN 2009 previously provided) because the primary aim of the study was to identify the effect of different methods of applying organic fertiliser. The other 23 studies were excluded and listed in Appendix 6 of our FSA report (published 29th July 2009) and Web table 4 of our AJCN publication (published 29th July 2009).

8. The primary reason for the exclusion of these 23 studies was the fact that they provided no direct comparison of the nutrient content of organically and conventionally produced foods. For example, many papers provided data comparing organic with integrated or hydroponic production methods. Neither integrated nor hydroponic is specifically conventional, and these papers were therefore systematically excluded in order to reduce heterogeneity in the definition of the primary exposures of interest namely organic and conventional farming practices. Other excluded studies provided information on the nutrient content of foodstuffs during conversion to organic farming systems, and these papers similarly failed to provide direct comparisons of nutrient content of organically and conventionally produced foodstuffs.

9. Despite strenuous efforts to identify all relevant papers which included contacting relevant trade bodies and researchers, we did not identify the four remaining papers (Abreu 2007; Anttonen 2006; Zafrilla 2003; Zhao 2007) on the list provided by the Soil Association and the Organic Trade Board in our systematic search process. For the benefit of the Sub-Group we attach the abstracts of these four papers (Unidentified abstracts attached). Without reading the full papers it is not possible to say whether these four studies are relevant or whether they would meet our pre-specified quality criteria.
Point 2

Secondly, the Sub-Group would like to invite you to comment further on the treatment of confounding factors. You discuss the importance of these factors in the first AJCN paper. The sub-Group would be grateful if you could comment in a bit more detail on how you ensured that the comparisons between nutrients in organic and conventional samples were done on a ‘like for like’ basis with regard to the many other confounding factors (for example variety, cultivar or breed; season, weather, location, and so on).

10. It is clear that there are many factors that influence the nutrient composition of natural foodstuffs. In order to explore the various sources of variability we drew an intuitive map at the start of our review process of the many factors that could potentially influence the nutrient content of foodstuffs (see Figure 1 of Systematic Review Protocol previously provided).

11. Many of the identified factors are, of course, not true “confounding” factors in the epidemiological sense, but rather factors that will increase variability in the outcome of interest, namely nutrient content. While it is possible to identify a few factors that are likely to be among the most important sources of variability (cultivar of crop/breed of livestock; fertiliser and crop protection regimens), it is currently not possible to quantify the relative importance of each potential factor.

12. To highlight this point we attach a recent research report on the polyphenol content of apples over a three year period from Prof. Bernhard Watzl’s group from the Max Rubner Institute in Germany (Stracke et al. 2009 attached). This paper reports that there were statistically significant differences between organically and conventionally produced apples in polyphenol content in one of the three study years, but importantly that year-to-year variations in polyphenol content were up to 20% larger than within year differences in production method. We bring this report to the Sub-Group’s attention as it clearly demonstrates that there is much still to learn about the various factors that influence nutritional composition of foodstuffs and that more-or-less uncontrollable climatic factors are likely to be important sources of variability.

13. We based our meta-analysis on published data and therefore allowed individual reporting scientists to define their own procedures for accounting for the factors that could increase variability (see Point B in letter to GACS Sub-Group dated 10th September 2010). The extent to which this was done, and the degree to which this was reported depended very much on the study design and on the quality of the research team. Meta-regression was not deemed feasible given the heterogeneity of the published evidence. We note that it is not the purpose of systematic reviews to improve the quality of published work. Rather to identify the totality of existing work relating to a specific research question, establish a ranking of quality of the published work, and synthesise in a pre-specified and standardised manner the findings of the body of available work.

14. Our systematic review identified data collected in three study designs each of which exerts a different level of control over the various factors that could potentially influence nutritional composition. Clearly, none of the studies provided data on all potentially relevant factors identified in our intuitive map and true “like-for-like” comparisons are not possible.

15. All 55 satisfactory quality studies included in our review provided information on the cultivar of crop or breed of livestock included in the analysis. With the exception of a small number of papers that reported the nutrient content of specified combinations of cultivars of wheat or rice, the analysis included in our review related to specified identical cultivars grown either organically or conventionally.
Third, the SA/OTB response included comments on a number of technical points relating principally to 'handling of variation in data reporting and data structure among different studies', reproduced below. The Sub-Group felt that it would be best to invite you to comment on these points directly.

16. We note the points raised by the Soil Association and the Organic Trade Board with respect to data handling.

17. Using a systematic search process we attempted to identify all relevant published studies reporting a direct comparison of the nutrient content of organically and conventionally produced foodstuffs. Decisions to include or exclude studies were based on pre-specified inclusion and exclusion criteria defined in our pre-specified peer-reviewed protocol published on-line on 18th April 2008. Similarly, the criteria used to define study quality were reported in our review protocol and published on-line on 18th April 2008.

18. The identified studies were very heterogeneous in nature and in order to reduce the variability in study design and outcome reporting we focussed, as requested by the Agency in their research specification (see Point 2i above) on those papers whose principal aim addressed our review’s pre-specified research question on nutrient content. We systematically excluded studies with the following primary research aims:
   - authentication studies – e.g. is laboratory method A better than laboratory method B in determining whether a foodstuff was organically produced?;
   - fertilizer studies – e.g. does fertilizer method A affect nutrient content in a different manner to fertilizer method B?

19. We similarly systematically excluded studies that did not report a relevant outcome. Such studies included those that:
   - did not report a direct comparison of the nutrient content in organically vs. conventionally produced foodstuffs;
   - did not report a comparison of nutrient content;
   - reported the content of contaminants in foodstuffs;
   - reported on the nutrient content of inedible portions of foodstuffs.

20. The purpose of systematic reviews is to identify and synthesise in a standardised manner the totality of the available evidence on a pre-specified research question. In our review we included all relevant reported data that met our inclusion criteria irrespective of the foodstuff under analysis. We note that arbitrary selection of individual foodstuffs would have limited the data available for analysis, introduced bias into our review and significantly impacted on the credibility of our findings.

21. The validity of meta-analyses is dependent upon the quality of the data available. In order to standardise the quality of the data used in our meta-analysis we excluded data from studies that reported their primary outcome data only in graphical formats from which it is not possible to obtain exact experimental values in a standardised manner.

22. We extracted data on more than 450 different nutrients and nutritionally relevant substances and because of the heterogeneity and quality of the extracted data were unable to use standard meta-analytical techniques (see Point E in letter to GACS Sub-Group dated 10th September 2010). We note that there are no standard techniques for handling data such as those extracted in the current review and we selected a clear and transparent method for meta-analysis to make best use of all available data.
23. We grouped nutrients into 98 categories and conducted analyses on the nutrient content of crops for those nutrient categories reported in 10 or more studies. To make best use of the more restricted database on livestock products we conducted analysis for those nutrient categories reported in 4 or more studies.

24. For papers that reported multiple tests on the same sample, we calculated and used the mean of the reported means as our data point. For papers that reported multiple outcomes from the same or similar samples we used all data points, but in the expectation that there would be correlations between multiple data points from the same study we calculated robust standard errors. Use of robust standard errors statistically allows for outcome clustering within individual studies thus removing any assumption of independence between data points from the same study.

25. We tested the distributions for normality and graphically reported all data points in Appendices 12 and 13 of our report to the FSA published online on 29th July 2009. We reported our analysis using an untransformed metric (% standardised difference) and following a request, repeated and re-reported our analysis in a letter to the AJCN using a metric that transformed the data (log of the response ratio).

26. We tabulated the results of our meta-analysis providing % standardised means, robust standard errors and p-values in the AJCN on the 29th July 2009. We highlighted the differences in nutrient content that were statistically significant (p<0.05). However, by providing both the % standardised mean differences and an estimate of variance around the sample mean we ensured that readers could review the strength of evidence themselves without relying solely on p-values (see Point E in letter to GACS Sub-Group dated 10th September 2010). We used the term “no evidence of a difference” no fewer than six times in our AJCN text to signify that based on systematic review of the totality of the currently available evidence there was no statistically significant evidence of differences in nutrient content for the majority of nutrients reported.