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Review of data on possible toxicity of GM potatoes

The Royal Society published a review of what was known scientifically about the suitability of GM plants for food use in September 1998. Because of the current controversy, we are looking again at several issues, and in particular we have reviewed all available data related to work at the Rowett Research Institute on the possible toxicity of genetically modified potatoes. Our main conclusions are as follows.

- 1 The safety of GM plants is an important and complex area of scientific research and demands rigorous standards. However, on the basis of the information available to us, it appears that the reported work from the Rowett is flawed in many aspects of design, execution and analysis and that no conclusions should be drawn from it.
- 2 We found no convincing evidence of adverse effects from GM potatoes. Where the data seemed to show slight differences between rats fed predominantly on GM and on non-GM potatoes, the differences were uninterpretable because of the technical limitations of the experiments and the incorrect use of statistical tests.
- 3 The work concerned one particular species of animal, when fed with one particular product modified by the insertion of one particular gene by one particular method. However skilfully the experiments were done, it would be unjustifiable to draw from them general conclusions about whether genetically modified foods are harmful to human beings or not. Each GM food must be assessed individually.
- 4 The whole episode underlines how important it is that research scientists should expose new research results to others able to offer informed criticism before releasing them into the public arena.

1. Background

In April 1999 the Royal Society convened a Working Group to examine whether newly publicised research required changes to our September 1998 statement *GM plants for food use*. This report deals with the apparent evidence that genetically modified potatoes adversely affected the health and growth of rats. The report has been endorsed by the Council of the Society, and was prepared by a group chaired by Professor Noreen Murray FRS, FRSE (University of Edinburgh). The other members were Professor Brian Heap FRS (Foreign Secretary and Vice-President of the Royal Society), Professor William Hill FRS, FRSE (University of Edinburgh), Dr Jim Smith FRS (National Institute for Medical Research), Professor Michael Waterfield FRS (Ludwig Institute for Cancer Research and University College London) and Dr Rebecca Bowden (Secretary).

2. Methodology

We sought information from all possible sources about the work at the Rowett Research Institute and obtained the following:

- Report of project coordinator, Arpad Pusztai FRSE, on data produced at the Rowett Research Institute (RRI), 22.10.98
- Audit of data produced at the Rowett Research Institute, 21.8.98, SOAEFD (Scottish Office Agriculture, Environment and Fisheries Department) flexible fund project RO818
- Response to request for clarification from the Rowett Research Institute
- Response to request for information from Dr Susan Bardocz
- Information provided by Advisory Committee on Novel Foods and Processes (including correspondence with Dr Stanley Ewen)
- Statistical analysis carried out by Biomathematics and Statistics Scotland of experiments on genetically modified potatoes conducted at the Rowett Research Institute, 1.3.99
- Minutes of evidence - Science and Technology Committee of the House of Commons, 8.3.99
- Response to request for information from Dr Vyvyan Howard of Liverpool University
- Response to request for information from Mr G Horgan of BLOSS
- Response to request for information from Professor John Gatehouse of Durham University
- Response to request for information from Professor Michael Wilson, Scottish Crop Research Institute
- Information from SOAEFD on rationale for research

Dr Pusztai indicated to us that further information existed, but did not provide it.

We sent the available information to six independent, impartial reviewers whose expertise included statistics, clinical trials, physiology, nutrition, quantitative genetics, growth and development, and immunology. Their remit was to examine the data that we gave them and advise us, in the usual way of referees, about the scientific merit of the work described. They were not asked to give an opinion on the actions of any individuals involved in this work.

This report is based on the responses from the six reviewers. The responses were copied to Dr Arpad Pusztai, who was given the opportunity to comment. In accordance with normal scientific practice, the reviewers remained anonymous.

Dr Pusztai suggested to us that his reports were internal Institute documents and that it was therefore not appropriate to peer review them. However, since they were released into the public domain, both through the media and on the Internet, it seems to us entirely appropriate that they should also be subjected to expert scientific scrutiny - all the more so because of the importance of this area.

We now examine two specific claims that have been made as a result of the Rowett work.

3. Did the GM potatoes tested have a specific effect on organ development and metabolism of the rats?

The experiments set out to investigate whether potatoes genetically modified to contain a lectin gene from a snowdrop affected the development of organs or the metabolism of the rats to which they were fed, in the short (10 days) or long (110 days) term. The structure of the experiments was changed as they progressed, which made comparisons between rats

fed on modified potatoes and those fed on unmodified potatoes more difficult. Some results showed differences in the overall body weights and in the weights of individual organs in the two groups of rats. However, such results as were statistically significant did not fall into a readily discernible pattern.

A particular difficulty is that the experiments were not well designed. For example, there is very little information about how the GM and control diets differed in their detailed composition, and in particular about differences other than those attributable to the inserted gene. These differences should have been fully analysed, and addressed by using several distinct strains of GM potato in the feeding trials. Second, the GM potatoes used contained almost 20% less protein than unmodified potatoes. Therefore, in the long-term feeding study, rats being given GM potatoes were also given additional protein to meet Home Office requirements intended to avoid starvation: observed effects could have been caused by this supplementary diet being inadequate or incomplete. Third, when a rat is underfed many organs are likely to be affected, so that separate measurements on the same specimen will turn out to be interrelated.

An added deficiency of the study was that, as far as we can tell, the measurements were not conducted 'blind' as is normal practice for trials of this kind (a protocol in which the scientists making the measurements are not aware of how the animals have been treated). Unconscious bias is well known to be a source of invalid results.

Because of the poor experimental design, it is simply not possible to be sure about the causes of the small effects obtained in the study.

4. Did the GM potatoes tested have a specific effect on the immune system of the rats?

It had been claimed that the consumption of GM potatoes had significant effects on the immune system of rats in the feeding trials, because of some effect of the genetic modification itself rather than because of the particular gene inserted. Reviewers were asked to consider if this conclusion was valid.

One of the immune reactions in the body can be mimicked in the laboratory. Antigen-reactive white blood cells (lymphocytes) are transformed into dividing lymphoblasts when they are stimulated by specific antigens. This provides a means of testing for effects on the immune system.

The claim that the Rowett data show evidence that the inserted gene had a different immune effect from simply adding lectins to unmodified potatoes does not stand up. Inappropriate statistical tests had been applied to the data and, when the appropriate comparisons are made, there are no interpretable differences. Moreover, the experimental data in this area are beset by the same sources of inconsistency noted in section 3 above.

5. Conclusions of review of data

The work on feeding trials with GM and non-GM potatoes attempted to cover too much ground with the resources available.

In the form currently available, the data reviewed provide no reliable or convincing evidence of adverse (or beneficial) effects, either of lectins added to unmodified potatoes or of potatoes genetically modified to contain a lectin gene, on the growth of rats or on their immunological function.

In summary, the data presented to the reviewers and Working Group are inadequate for the following reasons:

- poor experimental design, possibly exacerbated by lack of 'blind' measurements resulting in unintentionally biased results;
- uncertainty about the differences in chemical composition between strains of non-GM and GM potatoes;
- possible dietary differences due to non-systematic dietary enrichment to meet Home Office and other requirements;
- the small sample numbers used in experiments testing several diets (all of which were non-standard diets for the animals used) and which resulted in multiple comparisons;
- application of inappropriate statistical techniques in the analysis of results;
- lack of consistency of findings within and between experiments.

The uncertainty and ambiguity of the data urge great caution in the interpretation of the results presented. A much improved experimental design, with stringent controls, would have been needed if the claims made for the study were to be convincing. Even if the results of the particular study had

supported the claims that have been made for them, it would have been unwise to use them for making statements about the safety or otherwise of all GM foods.

Although we have no evidence of harmful effects from genetic modification, this of course does not mean that harmful effects can be categorically ruled out. This issue can be resolved only by the necessary research carried out to a high standard and by full use of the regulatory mechanisms for dealing with safety of food.

6. Future research

Reviewers were asked to give advice on the necessity of future research arising from the data presented.

The only way to clarify the current situation would be to refine the experimental design of the research done to date and to use this as the basis for further studies in which clearly defined hypotheses were tested, focused on the specific differences already claimed. It would be necessary to carry out a large number of extremely complex tests on many different strains of GM and non-GM potatoes. It would be important to ensure that these studies had sufficient statistical power (in the sense that numbers in each experimental group were sufficient to deal with the variability in individual response) to come to a clear conclusion. It would also be important to take adequate account of the age and the susceptibility of the animals and the wholesomeness, completeness and adequacy of the entire diet. Careful thought would have to be given to the specific targets for any hypothesised damage.

7. Recommendations

In view of the public interest in this case we recommend that the results of any future studies on testing GM food safety, when completed, should be peer reviewed and then published. This would provide an opportunity for the international scientific community and the public at large to have access to the information.

The Royal Society has recommended in its September 1998 statement *GM plants for food use* that any over-arching body analyse the current regulations, giving particular consideration to whether long-term animal feeding studies are necessary to provide greater information on allergenicity or toxicity. We now reiterate this recommendation.