

into GM food technology, including study of its potential effects on health.

These responses reflect an appropriately cautious approach towards the science of genetic modification. They reflect the real concern expressed by both "single-interest groups" and a wider public. These anxieties may seem odd, even irrational, given that GM foods were introduced in the USA without any sign of consumer anxiety. Why? Because Europe now lives in a post-BSE (bovine spongiform encephalopathy) age, one in which society has learned that the epidemic of BSE was brought on by unchecked industry-driven changes in farming practices and that the denials of risk by government and scientific authorities were worthless. That concern is now spreading beyond the UK. Recognition of this deeply ingrained public scepticism about food technology has led Monsanto to rethink its entire GM-food strategy.^{8,9}

The comments by Lachmann, Sykes, and Gosden are therefore disappointing because they reflect a failure to understand the new, and apparently unwelcome, dialogue of accountability that needs to be forged between scientists and the public. Risks are not simply questions of abstract probabilities or theoretical reassurances. What matters is what people believe about these risks and why they hold those beliefs. Ewen and Pusztai's data are preliminary and non-generalisable, but at least they are now out in the open for debate, as are the results, also published in today's *Lancet*, of Brian Fenton and colleagues. Only by welcoming that debate will the standard of public conversation about science be raised. Berating critics rather than engaging them—and criticising reports of research, as the Royal Society did with the Pusztai data, before those data were reviewed and published in the proper way—will only intensify public scepticism about science and scientists.

Richard Horton

The Lancet, London WC1B 3SL, UK

- 1 Lachmann P. Health risks of genetically modified foods. *Lancet* 1999; **354**: 69.
- 2 Editorial. Health risks of genetically modified foods. *Lancet* 1999; **353**: 1811.
- 3 Dobson R. Medical stars pack their bags. *Independent on Sunday* Sept 26, 1999: 16.
- 4 May R. Genetically modified foods: facts, worries, policies, and public confidence. London: Office of Science and Technology, 1999.
- 5 Lean G. Smeared GM expert vindicated. *Independent on Sunday* Oct 3, 1999: 1.
- 6 Royal Society. Genetically modified plants for food use. London: Royal Society, September, 1998.
- 7 Donaldson L, May R. Health implications of genetically modified foods. London: Department of Health, May, 1999.
- 8 Quinn S. Monsanto rethink welcomed. *Guardian* Sept 27, 1999: 4.
- 9 Finn G. Monsanto's U-turn on "terminator gene" seeds. *Independent* Oct 5, 1999: 1.

Adequacy of methods for testing the safety of genetically modified foods

See pages 1353, 1354

An issue that has been prominent in the current debate on the health risks of genetically modified (GM) foods is whether there are adequate methods of testing for the safety of these foods. One view is that the safety assessments of these foods are not as rigorous as those for new chemicals or drugs. Today's *Lancet* carries two Research Letters reporting work on the potential risks to human health of the lectin *Galanthus nivalis* agglutinin (GNA), a compound that may be useful in protecting

food plants from attacks by insects. These letters raise issues about the design of studies on safety.

Stanley Ewen and Arpad Pusztai report that, when fed to rats, GM potatoes containing the GNA lectin have proliferative and antiproliferative effects on the gut. They suggest that several of these effects are due to alterations in the composition of the transgenic potatoes, rather than to the newly expressed gene product. However, data on the composition of the different diets are not reported in the letter. Pusztai has released some of these details on the internet (<http://www.rri.sari.ac.uk/gmo/ajp.htm>). These details indicate that the content of starch, glucose polymers, lectin, and trypsin and chymotrypsin inhibitors in GM potatoes differed from that of the parental line. Unfortunately, these differences have not been examined further by analysis of an extended range of lines, for evidence on whether these differences are attributable to the genetic modification or to natural variations. Another shortcoming of the study is that the diets were protein deficient; they contained only 6% protein by weight. There is convincing evidence that short-term protein stress and starvation impair the growth rate, development, hepatic metabolism, and immune function of rats.^{1,2}

Ewen and Pusztai say that the significant differences between diet groups in variables such as mucosal thickness or crypt length are evidence of the biological effects of the GM foods. Such a claim is easy to make but difficult to prove, because no consistent patterns of changes were observed in the study. Ingestion of potatoes may be associated with several adaptive changes in the gut because of the low digestibility of raw or partly refined potato starch. In rats caecal hypertrophy is a common response to short-term feeding of various poorly digestible carbohydrates, such as raw potato starch.^{3,4} A physiological response of this nature is probably of little toxicological significance. Dose-response studies would have helped in the assessment of consistency of response.

The experiments done by Ewen and Pusztai were incomplete, included too few animals per diet group,⁵ and lacked controls such as a standard rodent diet containing about 15% protein (lactalbumin) as a balanced source of aminoacids⁶ and a test diet with potatoes containing an "empty" vector. Therefore the results are difficult to interpret and do not allow the conclusion that the genetic modification of potatoes accounts for adverse effects in animals. Similar criticisms of this work have been made by the Royal Society (http://www.royalsoc.ac.uk/st_pol54.htm).

In the second Research Letter, Brian Fenton and colleagues provide data that indicate strong binding of GNA to human white blood cells in vitro. Binding per se of a lectin does not automatically imply cell activation. Nevertheless, such findings emphasise the need for further studies. Attention should not be confined to the gastro-intestinal tract, but should also be paid to the bioavailability of these compounds and their potential toxic effects once they have entered the systemic circulation. Such investigations will be of paramount importance for future generations of GM foods (see below). An extensive toxicological study of this type has been done with a GM tomato containing an insecticidal protein derived from *Bacillus thuringiensis*.⁷

What about the adequacy of existing test methods and strategies for the assessment of the safety of GM foods?

Internationally agreed strategies for the evaluation of the safety of transgenic food crops with improved agronomic properties have been drawn up. The assessments have consisted of the characterisation of the new gene products, identification of alterations in concentrations of nutrients and known toxicants, and evaluation of the potential allergenicity of the gene product and of the implications of gene transfer between plants and the gut microflora of animals or human beings.⁸ The first approach to safety assessment is a comparative one—ie, a new food is compared with a conventional product that long-term experience has shown to be safe (concept of substantial equivalence).⁹ The data so far indicate that GM crops with agronomic advantages that have been introduced into the environment do not differ from the traditionally grown crops except for the inserted traits.

Safety testing will have to be adjusted for the “second generation” of food plants, which are modified to improve food-quality traits—eg, to raise the nutritional value of the proteins, to increase concentrations of oils low in saturated fats or of novel carbohydrates, or to fortify the foods with micronutrients or antioxidants. These must undergo extensive toxicological and nutritional assessment with a combination of in-vitro and in-vivo techniques as required for novel foods in general.¹⁰

Particular attention must be given to the detection and characterisation of unintended effects of genetic modification. Inferences about such effects can no longer be based solely on chemical analysis of single macronutrients and micronutrients and known crop-specific antinutrients or toxins. New methods have been developed to screen for potential alterations in the metabolism of the modified organism by analysis of gene expression (monitored by microarray technology, mRNA fingerprinting), by overall protein analysis (proteomics), and by secondary metabolite profiling.^{11,12} Depending on the outcome of these studies, further toxicological and nutritional studies may be needed.

In summary, methods to assess the safety of GM foods that are already on the market are adequate, but the future generation of such foods will need a wider range of tests covering both toxicological and nutritional endpoints. The studies must be designed carefully because of the complexity of foods.¹³ This complexity means that the adoption, as recently proposed,¹⁴ of an approach used for pesticides and food additives—the establishment of an “acceptable daily intake”—is inappropriate. Results of studies into GM foods should be interpreted with caution and presented to the scientific community in sufficient detail.

*Harry A Kuiper, Hub P J M Noteborn,
Ad A C M P Eijnenburg

RIKILT (National Institute for Quality Control of Agricultural Products), Wageningen University and Research Centre, Wageningen, NL-6700 AE, Netherlands

- 1 Konno A, Utsuyama M, Kurashima C, Kasai M, Kimura S, Hirokawa K. Effects of a protein-free diet or food restriction on the immune system of Wistar and Buffalo rats at different ages. *Mech Ageing Dev* 1993; **72**: 183–97.
- 2 Le Moullac B, Gouache P, Bleiberg DF. Regulation of hepatic transthyretin messenger RNA levels during moderate protein and food restriction in rats. *J Nutr* 1992; **122**: 864–70.
- 3 Walker R. Some observations on the phenomenon of caecal enlargement in the rat. In: Gali CL, Paoletti R, Vettorazzi G, eds. *Chemical toxicology of food*, vol 3. Amsterdam:Elsevier/North-Holland Biomedical Press, 1978:339–48.

- 4 Lopez HW, Coudray C, Bellanger J, Younes H, Demigne C, Remesy C. Intestinal fermentation lessens the inhibitory effects of phytic acid on mineral utilization in rats. *J Nutr* 1998; **128**: 1192–98.
- 5 OECD guideline for testing of chemicals 407. Repeated dose oral toxicity—rodent 28-day or 14-day study, adopted May 12, 1981. Paris:OECD.
- 6 Committee on Animal Nutrition, Board on Agriculture, National Research Council. *Nutrient requirements of laboratory animals*, 4th edn. Washington:National Academy Press, 1995:23.
- 7 Noteborn HPJM, Bienenmann-Ploum ME, van den Berg JHJ, et al. Safety assessment of the *Bacillus thuringiensis* insecticidal crystal protein CryIA(b) expressed in transgenic tomatoes. In: Engel K-H, Takeoka GR, Teranishi R, eds. *Genetically modified foods: safety issues*. ACS Symposium Series 605, Washington DC, 1995:134–47, 1995.
- 8 FAO/WHO. Joint FAO/WHO Expert Consultation on Biotechnology and Food Safety, Rome, 1996.
- 9 OECD. Safety evaluation of foods derived by modern biotechnology: concepts and principles. Paris:OECD, 1993.
- 10 Regulation (EC) no 258197 of the European Parliament and the council. *Official J European Communities* 1997 no L43, 1–7.
- 11 Van Hal NLW, Vorst O, Van Houwelingen AMML et al. The application of DNA micro-arrays in gene expression analysis. *J Biotechnol* (in press).
- 12 Noteborn HPJM, Lommen A, Van der Jagt RC, Weseman JM, Kuiper HA. Chemical fingerprinting for the evaluation of unintended secondary metabolic changes in transgenic food crops. *J Biotechnol* (in press).
- 13 OECD. Food safety evaluation. Paris:OECD, 1996.
- 14 Millstone E, Brunner E, Mayer S. Beyond “substantial equivalence”. *Nature* 1999; **401**: 525–26.

Does biocompatibility of dialysis membranes affect recovery of renal function and survival?

See page 1337

Despite the introduction of haemodialysis about 50 years ago, acute renal failure (ARF) is still a life-threatening illness, with a mortality rate of 40–80%.¹ Moreover, some studies have suggested that haemodialysis itself may delay recovery of renal function. The most controversial issues in the management of ARF by haemodialysis are the indications for and intensity of dialysis, the mode of dialysis, and the effect of biocompatibility of membranes on patients’ recovery and survival. The arguments put forward in the debate on the membranes have not always been strictly scientific.

In general, the complement-activating capacity of a dialysis membrane can be taken as an index of bioincompatibility. Complement activation leads to neutrophil activation and infiltration into the kidney. By releasing vasoconstrictors and damaging oxygen radicals, activated leucocytes may prolong renal damage,^{2,3} hence the view that the use of bioincompatible membranes might delay recovery from ARF.^{2,3}

There are data for^{4,10} and against^{11–15} this view (panel). In the early studies, by Hakim and colleagues⁴ in patients in intensive-care units, and by Schiffel and colleagues⁵ in patients who had undergone cardiac surgery, the use of Cuprophane (bioincompatible) membranes adversely affected survival rate, the occurrence of sepsis, the duration of oliguria, and the rate of renal recovery. Because of the higher mortality rates due to sepsis and the slower resolution of renal function in the Cuprophane group, Schiffel and colleagues⁵ prematurely stopped their study for ethical reasons. Yet they later published a follow-up report, which extended their earlier series of patients.⁶ According to the second report, gram-negative organisms were cultured from most of the patients with a positive blood culture who had been dialysed with Cuprophane, whereas only gram-positive bacteria were