Comments on GM Science Review

From Econexus, the Five Year Freeze, Friends of the Earth, GeneWatch UK, Greenpeace, the Soil Association, and Dr Michael Antoniou

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1. Generally, we welcomed the more open process of this review and in some important ways the review represents an important step forward in how scientific knowledge is presented. In explicitly acknowledging and describing more of the uncertainties in GM science than hitherto, as well as the attempt to document divergences in interpretation, the GM Science Review is the first to represent science for use in policy in this way. In this respect, and with some inevitable provisos, we consider the general model could be applied more widely in the future. However, we believe there is still a long way to go before a genuinely precautionary scientific appraisal of GM technology is completed and which the public clearly wish to see. There are a number of features and key themes that emerge form the report that we would take issue with:

2. First, the constant reference to 'case-by-case analysis' of the risks posed by GM and complete failure to examine the limitations of such an approach. These include that:
   - there are unique technological and conceptual problems with GM that are generic in nature which cannot be addressed on a "case-by-case" basis;
   - an exclusion of comparative assessments so that it is not possible to make choices between different options;
   - an inability to address generic questions about, say, the overall impacts of HT crops on patterns of herbicide use;
   - the emphasis on each individual GM crop is likely to lead to a lack of data on interactions between GMOs;
   - cumulative impacts are not adequately dealt with;
   - excessive emphasis is placed on the introduced trait which diverts attention from pleiotrophic impacts.

3. Second, the reluctance to acknowledge properly that GM poses huge new areas of uncertainty and the extent of our lack of knowledge. The failure to lay out and examine the limitations of science in section 6.8 is a striking example of this.

4. Thirdly, the use of 'no evidence' as a supposed indicator of no harm. The US National Academy of Sciences recently reviewed the regulation of the environmental impacts of transgenic plants[1] and said that (p10):'***The committee recommended that APHIS should not use the term "no evidence" in its environmental assessments****. The term "no evidence" can mean either that no one has looked for evidence or that the evidence provides contrary evidence. Lack of evidence is not typically useful in making regulatory decisions about risk'.* (emphasis in the original). We believe that this also applies to health assessments and urge the science review panel to abandon its use of 'no evidence' (e.g. Executive summary - 5.5; 6.3; 6.8 and elsewhere) in its review because of its ability to be misleading.

[1] National Academy of Sciences (2002) Environmental impacts of transgenic plants: the scope and adequacy of regulation. National Academy Press: Washington.

5. Fourthly, the lack of examination of what happens in practice with the risk assessment process rather than the theoretical process. This is most marked in chapter 5 on the safety of GM food and feed. This is particularly important given the lack of public confidence in government and industry in these matters as evidenced by the findings of 'GM Nation? the public debate'.

6. Fifthly, the lack of regard to alternatives and how these should be foremost in any evaluation particularly considering the public interest in whether GM crops are needed.

7. Sixthly, although the terms of reference said that divergence of views should be incorporated, there was a failure in many cases to do this. Examples include section 6.2 on invasiveness and section 7.5 on gene transfer to viruses.

Chapter 1 General Introduction

Main points

- The lack of past support (and reasons for it) for research into the environmental and health impacts is not discussed.
- Knowledge outside formal reporting systems has not been included which leads to the omission of important on-the-ground experiences.
- A failure to connect the findings of the Science Review with the practice of the scientific advisory system.

1.3 How is scientific knowledge acquired

8. The description of scientific process leaves out the decisions involved in why particular research is carried out. No scientists are completely free to choose their research topics. Any significant project requires funding and that means producing grant applications. These grant applications are assessed by funding bodies, either in the public or private sector. Thus the actual projects that scientists undertake are those that the funding bodies, with their own priorities and interests, deem worthy of funding. This means that the knowledge base of science in this area (and many others) is determined by the priorities and interests of the funding bodies. In turn this means that significant areas of knowledge do not get prioritised. It is our observation that there is very little conclusive and comprehensive science on the way that GM crops have performed in the US, nor the incidents that have indicated how GM crops are grown and how they perform in the real world. It would appear that this is not a priority area for funding despite it having considerable interest and relevance to our understanding of the issue. (see below)

9. In examining the evidence used for the review, the cited references show that this has been peer-reviewed literature (or more accurately, material that has been published in journals where papers are peer-reviewed), government or international agency (e.g. FAO, OECD) reports, conference proceedings and books from academic-type publishers. Therefore, findings that were considered acceptable to the review were not 'evidence' but conventionally-understood sources of scientific authority. The absence of funding for research projects dealing with some important parts of the debate means that the heavy focus on peer-reviewed literature can miss important aspects of current and emerging

knowledge. Examples include: the Starlink contamination incident[2]; the Advanta seed contamination incident[3] in Canada that caused contamination of seed in Europe; failure of Roundup Ready cotton in Mississippi[4]; and the use of atrazine on Liberty Link maize[5]. Broadening the range of evidence considered by the review should most emphatically not mean that opinion could be accepted as fact. But it would mean including relevant evidence from the real world which might cast scientific knowledge in a fresh or new light, or illustrate the contingencies around knowledge. In practice, the Review did use this approach in one very high-profile example, the apparent absence of reported health effects from consumption of GM foods in the US despite the absence of any peer reviewed literature on the subject. Indeed, it is curious given the emphasis on peer-reviewed literature how this anecdotal finding was the only 'fact' reported in the first few paragraphs of the press release announcing the first report. We conclude from that, not that peer-review is essential for consideration in the Review, but that the use of real-world information is currently partial and inconsistent.

1.6 What is the relationship between this review and the work of the statutory advisory committees on GM?

10. A crucial part of this review has been that it has identified areas of uncertainty not acknowledged, certainly not explicitly, in the approval process. If the lessons about the generic uncertainties about GMOs are not absorbed and acted upon by the statutory committees then this review will not have effectively fulfilled a key part of its mandate. What remains unexplored is, for example, how ACRE can take account of the generic lack of knowledge about ecological processes and systems, and our dearth of knowledge about soil ecology in coming to conclusions about particular GMO release applications. The actual difference between theoretical risk assessment and what happens in practice is the main subject of our comments on Chapter 5, but these can be extrapolated equally well to environmental evaluations.

Chapter 2 Methodology

Main Points

- The format of the review and explicit recognition of uncertainty is important and welcome although the presentation of uncertainty was often limited and partial.
- The panel had a pro-GM bias and the inclusion of the chairs of the GM advisory committees led to a lack of critical reflection on the actual conduct of the risk assessment process and what is accepted as evidence of acceptable risk.
- External to the Science Review, disgraceful pressure was placed on sceptical members of the Panel and Professor King acted properly to reveal this.
- Coordination with the public debate was limited and the Review Panel did not have sufficient expertise to understand public concerns.
- One important question – whether GM was needed in the light of alternatives – was not addressed even though it is a major strand of public questioning.

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[2] See for example David Barboza, 10 June 2001, New York Times, As Biotech Crops Multiply, Consumers Get little Choice http://www.mail-archive.com/ecofem@csf.colorado.edu/msg08236.html

[3] http://news.bbc.co.uk/1/hi/uk/753401.stm

[4] Union of Concerned Scientists newsletter, The Gene Exchange, Summer 1998 http://www.ucsusa.org/publication.cfm?publicationID=276

[5] http://news.bbc.co.uk/1/hi/programmes/newsnight/archive/2067669.stm

2.3 The Science Review Panel

11. It would appear that there was a considerable bias in favour of the technology in the membership of the panel given that a number of those appointed were already in some way connected with the GM approval process. There were two **members** from the bio-industry (compared with two **nominations** from the NGOs). Early invitations to members of four NGOs (Friends of the Earth, GeneWatch UK, Greenpeace and the Soil Association) were withdrawn because they were sent due to an administrative error. We were disturbed at this blatant bias in favour of the biotechnology industry.

12. An analysis of the membership of the panel shows that at least 9 [6] can be described, at least to those reasonably familiar with the issue, as advocates for the use of GM technology, whilst those who would probably describe themselves as sceptical (no-one on the Panel could be described as 'anti-GM') number just 4[7]. Many of the members of the Science Panel are well-known to members of NGOs who have been working on the GM issue for a number of years. Only 6 [8] appear to be new to the public debate over GMOs.

13. There are several potential implications of the panel make-up:
    - Having the chairs of the advisory committees made it unlikely that the way in which GM crops and foods would be evaluated *in practice* would be adequately scrutinised. This has proved to be the case (see comments on Chapter 5 for a detailed analysis).
    - A very limited range of perspectives was available so a proper assessment of the state of knowledge would not be undertaken. This has proved to be the case in some instances (see in particular comments on 6.2; 6.8 and 7.5). In the future, a proper peer review system is needed to complement what is an inevitably restricted range of expertise.
    - A bias in the way in which information would be presented. The emphasis on the use of 'no evidence' is one clear example of this.

14. Section 2.3 also refers to the spectrum of opinions on GM being included. Here we would like to register our shock at the disgraceful pressure exerted on members of the panel, apparently in connection with their sceptical views on GM. Press comment drew attention to the fact that, as recorded in the minutes of the Panel meetings, Dr Stirling's professional standing came under pressure for his approach on the Science Review. We are grateful to Professor King in his role as chairman of the Review for ensuring that this was not 'hushed up'. However, Professor Carlo Leifert reportedly also felt under pressure for his views[9], although he himself openly accepts that there was no firm evidence for this. This begs the question how genuinely open a process such a review can be when those who are not toeing the 'pro-GM' line feel their careers are threatened because of their legitimately sceptical interpretation of existing evidence.

2.4 Open meetings

15. The open meetings were part of the review but some have been roundly criticised for bias. The Royal Society meeting on gene flow came in for particular criticism

[6] Mike Wilson, Chris Leaver, Mike Gale, Mike Gasson, Andrew Cockburn, Simon Bright, Alan Gray, Janet Bainbridge, Phil Dale
[7] Andrew Stirling, Julie Hill, Mark Avery, Brian Johnson
[8] John Gray, Peter Young, Pat Heslop-Harrison, Diana Bowles, Bernard Silverman, William Sutherland.
[9] Interview on Today Programme, 19 September 2003

for being biased and for pro-GM comments being given much more latitude than comments questioning the merit of GM crops in terms of whether they were considered 'scientific' and relevant or not[10].

2.5 Strand co-ordination

16. Attempts to co-ordinate the three strands of the GM dialogue are referred to and for the science review the interaction with the steering board was through the participation of Phil Dale. At a more fundamental level, the expertise on the panel able to deal with the framing issues of the Science Review to ensure it was 'driven by public concerns' remains questionable. Malcolm Grant, chair of the Public Debate Steering Board, suggested several people[11] who could provide the necessary specialist insight to deal with appraisal of uncertainty, which was clearly one of the 'public concerns' issues that needed attention. However, the only person from this list of 4 suggestions[12] to be appointed to the Panel was Dr. Stirling, who was a nomination from the NGOs. In our view this left a capacity gap, not in the formal mechanisms of co-ordination but in the skills and experience to understand and incorporate the lessons learned from such an interaction.

2.6 The framework of the review

17. In general, the GM Science Review Panel is to be commended for attempting to rigorously document the levels of uncertainty and lack of knowledge in different parts of the body of empirical knowledge that makes up the science base. Our criticisms of how full that acknowledgement remain but that does not mean we do not recognise that using a format that explicitly attempted to do so was an excellent way to proceed.

2.7 The review of public concerns (the Corr Willbourn report)

18. Although being driven by public concerns was given as being the remit of the panel, it is clear from the Corr-Wilbourn research, and other work on risk acceptability, that a key element is the availability of alternatives (Question C1 – "Why do it? Why change what we've got? Is there a need for it?……."). This would involve an examination of the options available for agricultural improvement - although the definition of what constitutes 'improvement' in agriculture is now contested. Old assumptions about the need to continue to improve yields at the expense of biodiversity and through more intensive inputs are no longer widely held. Nor is it obvious that any desire to improve yields and food security in developing countries would best be met through genetic engineering; indeed there is substantial evidence that low-tech approaches would deliver much better results[13]. Alternatives to the goals of programmes of GM crops were not explored. So this question arising from the Corr-Willbourn report was not addressed. Whilst we would accept that this would be a huge project in its own right, and would require a whole new range of disciplines to be drawn upon, it remains an unanswered question about the purpose of GM crops. Essentially the terms of reference of the review were a more in-depth analysis of

[10] Les Levidow, Open University, http://www.gmsciencedebate.org.uk/topics/forum/0070.htm and Greenpeace letter to Royal Society, 12 Feb 2003, available on request.
[11] Letter to Prof David King, 16 September 2002, "GM Debate: the Science Strand"
[12] The others being Brian Wynne, Brian Collins and Steve Rayner.
[13] Parrott, N. and Marsden, T., (2002) 'The Real Green Revolution', Report from Cardiff University to Greenpeace Environmental Trust.

the range of issues covered by the existing scientific regulatory committees (ACRE & ACNFP).

19. The interpretation of 'driven by public concerns' was drawn attention to by a letter from the Royal Commission on Environmental Pollution which pointed out the difficulty of having a review in advance of the public debate which started in June. We would concur. Developing a second report at this stage addresses this to some extent but does not fully deliver the Royal Commissions's recommendation that people's values need to be taken into account "from the earliest stages of defining the problem and framing the questions that need to be addressed".

Chapter 3 The role of science in the regulatory process

20. For those not familiar with the references cited here it would be useful for the Review to elaborate on the limitations of risk assessment that are documented. For example, the subjective nature of the 'framing assumptions' behind any risk assessment process, the frequent failure to consider wide sources of expertise and the common failure to give due weight to ambiguities and unknowns. These are not problems unique to GMOs as similar shortcomings of risk assessment processes have been found in relation to hazardous chemicals, the effects of low-level radiation on health, and the fate of radionuclides in the environment.

3.1 Substantial equivalence

21. This 'principle' of substantial equivalence should be abandoned because its shortcomings (documented in the Royal Society of Canada report) and its shifting interpretation[14,15] show that it serves no useful purpose. Testing for safety (where the need for a GM food has been accepted) should include a full analysis of toxicological, allergenic and immunological effects and not just an analysis of chemical similarity. Although the Review accepts some of these points in principle it does not go on to accept that, because substantial equivalence has shifted in meaning and interpretation so significantly, continuing to employ the same terminology is more confusing than helpful.

3.2 The Precautionary Principle

22. The review discusses the precautionary principle and argues that the GM Science Review process embodies characteristics of a genuinely precautionary approach. It also lists 8 characteristics in Box 3.1 of a 'precautionary approach'. It seems that these characteristics were adhered to in varying degrees during the GM Science Review process. Adherence, in part, to some of these may well explain why this Review seems to have been seen as more cautious than in the past

23. Below the list of characteristics from Box 3.1 of the Review is reproduced with some comments attached:
    - *Inclusion of diverse scientific disciplines*: although the panel contained a number of different disciplines there remained an emphasis on molecular biology, little practical farming expertise, or anyone with consumer/food policy expertise. Also (see above re section 2.5) there was a paucity of people who

[14] Les Levidow and Joseph Murphy, 'The Decline of Substantial Equivalence: how civil society demoted a risky concept', Paper for conference at Institute of Development Studies, 12-13 December 2002, 'Science and citizenship in a global context: challenges from new technologies'
[15] Piet Schenkelaars, 'Rethinking Substantial Equivalence', Nature Biotechnology 20 p.119, 2002

could provide insight into handling the tricky area of uncertainty. See also comments above regarding panel membership.

- *Careful treatment of evidence so that absence of evidence of harm is not presented as evidence of absence, associated with a shift in levels and burdens of proof* – see following sections regarding comments on missing evidence of safety to environment and human health. Examples include: from chapter 6 failure to document the uncertainties over the extent to which an introduced trait determines invasiveness, and the limitations in the PROSAMO experiments because of known difficulties in determining whether alien species are invasive – indeed alien species often fail to establish before showing significant population growth. Other examples are given in our introduction above, where the inappropriate reliance on 'no evidence' was raised.
- *Open acknowledgement of uncertainty, ambiguity and gaps in knowledge in order to avoid concealing subjective judgement and the intrinsic limitations of risk assessment* – as stated above the GM Science Review made a welcome departure from conventional governmental analyses by attempting to do this. It acknowledged that "even a single gene inserted via GM techniques can produce a plant phenotype of which there is little or no experience" and that, therefore, there are forms and sources of uncertainty that are different and special to GM. However, the application of this understanding to the substantive part of the Review has been rather patchy, as can be seen from the comments below. Also pertinent here are the comments on the peer review focus of the Panel's work (see above in comments on section 1.3).
- *Transparent documentation of any assumptions and value judgements and an exploration of their scientific consequences by means of techniques like sensitivity and scenario analysis* – The framework adopted to analyse levels of uncertainty was a good start, but neither of the specific techniques of sensitivity testing or scenario analysis appear to have been used.
- *Involvement of stakeholders, lay people & participatory techniques to help ensure that 'framing assumptions' explored in scientific analyses are consistent with wider social issues and values* - The GM Science Review was a notably better exercise in an attempt to do this than before. However see comments above concerning sections 2.5 'co-ordination' and 2.7 'driven by public concerns', second paragraph.
- *Systematic and balanced assessment of pros and cons associated with a series of different options rather than focusing on the acceptability of a single option in isolation or a comparison between this and existing tolerated poor or worst practice* – again see first paragraph above to section 2.7 'Driven by Public concerns'. See also second paragraph above on section 2.6.2 Checklist regarding the baseline for comparison assumed.
- *Ensuring the appraisal process allows expression of balanced array of opinions free from coercive pressures and as independent as possible form particular financial or political vested interests* – see above in comments on section 2.3 on composition of the Panel, and episodes of pressure on members.
- *Serious consideration of issues such as irreversibility, flexibility of responses, diversity of policy options and the ease with which the associated commitments may be withdrawn to ensure strategies are as robust as possible in the face of new knowledge and surprise.* – The GM Science Review chose not to look at these issues, although the flexibility of agronomic options available, and the reversibility of the effects of GM releases (dealt with indirectly under invasiveness) are well within the technical terms of reference originally laid out for the review.

Chapter 4: How reliable is GM plant breeding?

Main points

- This chapter starts by misconstruing the key question. What the public wishes to be answered is not a technical question about the relative facility of GM versus other methods of plant breeding but in contrast is a question of safety. It is: do scientists properly understand what they are doing, from a risk perspective, when they genetically engineer a generic GM plant? *Confidence in scientists' ability to answer affirmatively is not likely to improve if they cannot appreciate the basis of public concern.*
- Relative discard rates (of GM compared to conventional breeding) are constructed as a measure of safety although there is no evidence to support this.
- It is claimed falsely that scientists and plant breeders universally support the current regulatory procedures.
- GM crop technology is not placed within the context of our current understanding of genome structure, organisation, function and regulation. From an informed perspective of genetics, GM possesses inherent major technical and conceptual flaws which lead to GM's high failure rate and the appearance of unexpected and unpredictable outcomes that can include poor crop performance and disruptions to biochemical composition.
- The references quoted in this chapter do not support the contention that other breeding methods result in crops that are as risky as GM plant breeding, in fact they contradict it. So also do all other comparisons of the relative contributions of various plant breeding methods, because they demonstrate that the methods described as risky are not widely used.
- This chapter uses flawed logic. It argues that because GM plant breeding has some similarities with conventional plant breeding methods it therefore carries no greater risks. Space flight has some similarities with commuter flights but no-one argues that it carries similar risks!
- Ultimately, Chapter 4 fails to make the case that GM plant breeding is safe. It tries instead to imply that other plant breeding methods are not safe. We agree that non-GM plant breeding methods can also produce potential health problems. However, we contend that the unique technical and conceptual features of GM raise novel safety concerns. This chapter fails to establish the relative risks between GM, traditional plant breeding and more recent techniques and it fails even to discuss the peer-reviewed literature describing the genetic damage associated with plant transformation and tissue culture.
- There are unique technological and conceptual problems with GM that are generic in nature. Therefore, an assessment of GM crops solely on a "case-by-case" basis is inappropriate.
- Marker assisted breeding is a more powerful and generally acceptable way forward for the use of biotechnology in agriculture.

The overall theme and perspective is potentially misleading

24. It is encouraging that an official Government document acknowledges that the use of GM in plant breeding possesses inherent unpredictability; for example:
    - Section 4.3.1, page 53: "Some reason that the long history of plant breeding means that phenotypic variation typically falls within a familiar range, yet even a single gene inserted via GM techniques can produce a plant phenotype of which there is little or no experience (Dale and Irwin, 1998)."

- Section 4.4, page 56, line 7: “It is also widely accepted that there is the potential for quite novel molecular interactions, which may fall outside our current scope of knowledge.”
- Section 4.6, paragraph 2: “However, as has already been noted above, the GM process does introduce certain novel sources of uncertainty. The degree of uncertainty is related to our ability to detect and interpret changes at a molecular level.”

25. However, the dominant theme of this chapter is set by the opening two sentences of the first paragraph (section 4.1, page 49): *“*Some people have expressed concern that GM plant breeding is too unreliable and imprecise for crops to be used in agriculture at all or at least without more extensive testing. *A principal argument used is that it is necessary to produce about 100 GM plants to obtain one that has desirable characters [sic] for use as a basis of a new GM crop variety”* (emphasis added). As a result the majority of this chapter is taken up with making a comparison between GM and non-GM methods for the development of novel crop plant varieties. This comparison is predominantly made by looking purely at agronomic performance as the endpoint rather than dealing with basic genetics principles.

26. The overriding conclusion upon which the use of GM in agriculture is justified, appears to rest on the assertion that GM may be imprecise but it is less uncertain than other methods of plant breeding. This overall perspective that is chosen for this chapter is not only surprising but also results in:
    - detracting attention from fundamental, generic technical and conceptual differences between GM and non-GM methods (especially natural sexual reproductive processes) and
    - fails completely to place GM within the context of our latest understanding of gene organisation and function within higher forms of life (plants, animals and humans).

27. The concerns that have been raised about GM food production and especially GM crop varieties have never been as to whether this technology is “reliable” or asked “does GM work?” as a method of plant breeding. Worries have stemmed from the unique technical features that are involved in GM procedures that give rise to novel safety considerations with respect to human/animal health and the environment. The “reliability” of GM to produce a desired agronomic outcome (e.g. specific herbicide resistance) has not been questioned. The concerns are as to whether, in achieving these agricultural objectives, host biochemistry has been disturbed such that it poses new actual and potential health and environmental problems. Therefore, the opening statement “*A principal argument used is that it is necessary to produce about 100 GM plants to obtain one that has desirable characters [sic] for use as a basis of a new GM crop variety”* is inaccurate, misrepresents the scientific concerns that have been raised and is, therefore, potentially misleading.

28. The use of agronomic criteria to assess GM as presented in this chapter continues to hold onto the now outmoded view that genes are isolated units of information, which as a result can be moved between organisms with totally predictable outcomes. Experience with GM plant research and crop performance within an agricultural context tells us that this is simply not the case. Contemporary understanding of genome organisation and regulation in higher organisms (plants, animals, humans) now explains the uncertainty associated with GM crop technology and highlights why this approach in its current form is both technically and conceptually flawed.

GM and contemporary understanding of genome organisation and function

29. Current models of genome structure state that genes are organised into "functional domains"[16]. The activity of genes both within and between functional domains is tightly regulated; functional domains can be in an active "open chromatin" or inactive "closed chromatin" configuration. What is very clear is that no gene works in isolation; gene position within the genome is crucial for appropriate regulation within an interconnected network of functions; organism diversity arises predominantly from multigene interactions rather than from single gene functions. With the discovery of a complex *epigenetic* code (DNA and histone/non-histone protein modifications), a given genetic function consists of more than just its protein coding DNA sequence[17]. The importance of epigenetic as well as genetic factors in determining gene identity and function is perhaps best illustrated by recent discoveries linking disturbances in the "histone code" with oncogenesis[18]. This complex state of genome structure/function was succinctly summarised by Craig Venter: "*In everyday language the talk is about a gene for this and a gene for that. We are now finding that that is rarely so. The number of genes that work in that way can almost be counted on your fingers, because we are just not hard-wired in that way." Craig Venter, Celera Genomics, 12 February 2001.*

30. Natural sexual reproduction methods of plant breeding preserve the complex gene organisation and regulatory networks that have evolved over vast periods of time. Therefore, from a fundamental genetics basis, the claim that natural sexual reproductive processes are "precise" is quite valid, since in bringing about new combinations (not "recombinations" as stated; page 50, paragraph 3, line 3) of gene functions *within* a species' gene pool, genomic order and control are maintained.

31. Although it is acknowledged that GM involves cross-species gene transfers and brings about the random insertion of the transgene into the host plant genome (section 4.3.2, paragraph 2), the consequences of this process from a basic genetics perspective as outlined above are considered very superficially or not at all. GM removes genes out of their normal context and randomly inserts transgenes into a totally new genomic environment and usually a foreign organism; this accounts for so called "position effects" where the efficiency with which a transgene will function is totally dependent upon its site of integration and the influences that will impinge upon it from the surrounding chromatin. Therefore, from the viewpoint of our understanding of gene organisation and function GM is "imprecise" and explains why the vast majority (at least 99%) of plant transgenic events are failures, despite the fact that strong ubiquitously functioning promoter/enhancer elements (e.g. CaMV) are used to drive transgene expression.

32. The disruption of host gene function by random transgene insertion with undesirable outcomes is also far from fully considered given the vast body of experimental evidence that highlights these potential dangers. In this context it is

[16] See Dillon, N., and Sabbattini, P. (2000). Functional gene expression domains: defining the functional unit of eukaryotic gene regulation. *Bioessays*. **22**: 657-665.
[17] See Dillon, N. (2003). Gene autonomy: positions, please... . *Nature* 425: 457.
[18] Plass C. (2002) Cancer epigenomics. *Hum Mol Genet*. 11: 2479-2488.

important to note that the promoter/enhancer genetic control elements (mostly 35S CaMV) that are used to drive expression of the transgene, do not possess an inherent dominant chromatin opening capability; that is, they are unable to establish their own transcriptionally active "functional domain". Expression of both the antibiotic resistance marker gene as well as the novel trait transgene is, as a result, totally dependent upon fortuitous integration events into regions of chromatin that are already open and active. Therefore, the procedures employed during GM ultimately *select* for transgene insertions into regions of the genome where other genes reside and which are being transcribed thereby *maximising* the probability of disrupting host gene order and function.

33. The mechanisms by which gene-function of the host can be disturbed by the transgene are at least three-fold. Firstly, host gene function may be lost due to transgene insertion within either the protein-coding region or a crucial transcriptional regulatory element. Secondly, the powerful enhancer component of the CaMV control element may upregulate expression of a nearby gene or genes. This is particularly important if the genes in question usually show a tissue-restricted expression pattern since the ubiquitously acting CaMV enhancer will, in all likelihood, induce inappropriate expression at ectopic tissue sites. Thirdly, the transgene may inadvertently compete for or interfere with genetic regulatory elements that co-ordinate expression from multigene loci; that is, the mere presence of a foreign transcription unit within a locus can disrupt the expression of many genes[19] (see Fraser and Grosveld, 1998). The following two studies help to illustrate the above imprecision and uncertainties of GM technology:

    - Shewmaker CK, et al. (1999) Seed-specific overexpression of phytoene synthase: increase in carotenoids and other metabolic effects. *Plant J*. 20: 401-412. This investigation attempted to increase carotene (Vit A) in rapeseed oil; a bacterial phytoene synthase (crtB) gene was overexpressed in a seed-specific manner. The desired outcome was achieved with a 50-fold increase in carotenoids in the seeds. However, quite unexpectedly there was (i) a significant decrease in tocopherol (Vit E), (ii) fatty acid composition was significantly altered and (iii) chlorophyll levels were reduced in developing seed.

    - Elmore, RW, et al (2001) Glyphosate-Resistant Soybean Cultivar Yields Compared with Sister Lines. *Agron. J*. 93: 408-412. This study consisted of side-by-side field trials over a 2-year period at 4 different locations of GM and equivalent non-GM varieties of glyphosate-resistant (GR) soybean cultivars. The authors' conclusions were: "Yields were suppressed with GR soybean cultivars..... . The work reported here demonstrates that a 5% yield suppression was related to the gene or its insertion process and another 5% suppression was due to cultivar genetic differential. Based on our results from this study and those of Elmore et al., 2001[20], the yield suppression appears associated with the GR gene or its insertion process rather than glyphosate itself."

34. These studies serve to illustrate a number of important issues. Firstly, the problems observed in both the above examples and the soybean study in

[19] Fraser P and Grosveld F. (1998) Locus control regions, chromatin activation and transcription. *Curr Opin Cell Biol* **10**: 361-365.
[20] Elmore, R.W., et al. (2001) Glyphosate-resistant soybean cultivar response to glyphosate. Agron. J. **93**: 404-407

particular, are caused by disturbances in multiple gene functions showing that the insertion of a single transgene at a single location within the host genome can disrupt either directly or indirectly the functions of many genes. Secondly, and perhaps of greater importance is that in the case of the GM soybean study problems of reduced yields ("yield drag") emerged only after commercial release and entry into the food chain[21]. This clearly demonstrates that major problems with GM crops - whether these may be agronomic performance, animal/human health or environmental in nature - can avoid being detected at their developmental phase and surface at a much later post-approval and release stage.

35. Surprisingly, the site or sites of transgene integration within the host genome is still rarely determined and, perhaps of greater concern, there is no obligation to do so from the regulatory authorities responsible for assessing the safety of the release of GMOs into the environment and their use as human and animal foodstuffs.

36. The use of tissue-specific promoters (Page 55, paragraph 2) may partly eliminate one concern, namely the induced ectopic expression of host genes when employing ubiquitous promoter/enhancer elements such as CaMV, but is still prone to all other problems resulting from transgene insertional mutagenesis described above.

37. Targeting transgene insertion (section 4.7, paragrapgh 1) is again an interesting future development that tries to partly address problems associated with random integration. However, what is said in this section is at present largely irrelevant, as all currently grown and proposed GM crops do not employ this approach.

38. Encouragingly, future research that is proposed in section 4.8 acknowledges the complexity of the genome and that genes function within the context of diverse but interconnected networks. The use of techniques that try to analyse organisms as a whole such as molecular (genomics, transcriptomics, proteomics) and metabolic (metabonomics) profiling as well as the role of epigenetic states (DNA methylation patterns and the histone code), should provide insight into basic biological processes and the effects of genetic alterations through GM and other procedures.

Flaws in the comparison between GM and non-GM plant breeding methods

39. The fundamental argument underlying Chapter 4 is that other methods of plant breeding are equally risky. To make this argument (essentially a comparison with existing worst practice) it is necessary to show that conventional methods are risky in the first place. Among conventional breeding methods there are a number that are associated with a likelihood of large scale genomic mutations and alterations. These include mutagenesis, tissue culture that includes a dedifferentiated stage and possibly wide crosses. These techniques are not risk-free and varieties created using them are sometimes harmful to eat or show unusual or unfortunate characteristics. Chapter 4 presents no evidence that

[21] See also Benbrook, CM (2001) Troubled Times Amid Commercial Success for Roundup Ready Soybeans: Glyphosate Efficacy is Slipping and Unstable Transgene Expression Erodes Plant Defenses and Yields. Northwest Science and Environmental Policy Center Sandpoint Idaho; http://www.biotech-info.net/troubledtimes.html; Fernandez-Cornejo J and McBride WD (2002) Adoption of Bioengineered Crops. USDA ERS Agricultural Economic Report No. AER810. 67 pp; http://www.ers.usda.gov/publications/aer810/).

molecular marker assisted breeding or TILLING are hazardous in any way and there is no reason we know of to suggest that they are. Of the remaining techniques, the hazard that they present derives presumably from random genetic changes caused by mutagenesis and tissue culture but their significance is uncertain - it may or may not be as significant a problem as it is for GM plant breeding.

Genomic changes resulting from transformation

40. Chapter 4 does not acknowledge adequately the importance of estimating the extent of genetic damage resulting from tissue culture and transformation. It briefly acknowledges some of the work done and describes it as inconclusive (4.5). We disagree. A large body of evidence exists which suggests that plant transformation causes very considerable genome-wide genetic damage. We summarise it below.

Somaclonal mutations and plant transformation

41. Populations of transformed plants show a high frequency of unexpected heritable phenotypes and wide variation in agronomic characteristics, such as alterations in plant height and yield[22]. Unexpected phenotypic changes are observed whether plants are produced via *Agrobacterium*-mediated transformation procedures or particle bombardment. Some of the observed changes may result from the use of tissue culture and some may result from the transformation process[23]. Recently researchers have begun using molecular techniques such as RFLP, RAPD, AFLP and RAMP in an attempt to quantify the magnitude of the genomic changes resulting from tissue culture and/or transformation. These techniques allow comparison of DNA polymorphism between transformed lines and non-transformed parental lines and estimate unintended genomic change occurring during plant transformation.

Agrobacterium-mediated transformation

42. Both phenotypic (e.g. leaf shape differences) and genotypic changes were observed in poplar plants which had undergone *Agrobacterium*-mediated transformation and tissue culture regeneration[24]. RFLP, RAPD and microsatellite analysis was used to look for polymorphisms. Each of 17 transformed plants

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[22] Bregitzer P, Zhang S, Cho M-J, Lemaux PG (2002) Reduced somaclonal variation in barley is associated with culturing highly differentiated, meristematic tissue. *Crop Sci* 42: 1303-1308.; Dale PJ, McPartlan HC (1992) Field performance of transgenic potato plants; Larkin PJ and Snowcroft WR (1981) Somaclonal variation- a novel source of variability from cell cultures for plant improvement. *Theor Appl Genet* 60: 197-214; Shu Q-y, et al (2002) Agronomic and morphological characterization of *Agrobacterium*-transformed Bt rice plants. *Euphytica* 127: 345-352.; Schuh W et al (1993) The phenotypic characterisation of R_2 generation transgenic rice plants under field conditions. *Plant Sci* 89: 69-79; Wu DX, Shu QY, Wang ZH, Cui HR, Xia YW (2002) Quality variations in transgenic rice with a synthetic *cry1Ab* gene from *Bacillus thuringiensis*. *Plant Breeding* 121: 198-202; Wang G, Castiglione S, Chen Y, Li L, Han Y, Tian Y, Gabriel DW, Han Y, Mang K, Sala F (1996) Poplar (*Populus nigra* L.) plants transformed with a *Bacillus thuringiensis* toxin gene: insecticidal activity and genomic analysis. *Transgenic Res* 5: 289-301.

[23] Coury DA and Feldman KA (1998) T-DNA insertion mutagenesis and the untagged mutants. In: Jain, Brar, and Ahloowalia (eds.) *Somaclonal Variation and Induced Mutations in Crop Improvement* pp. 517-538. Kluwer Academic Publishers, Dordrecht; McNevin JP, Woodward W, Hannoufa A, Feldmann KA, Lemieux B (1993) Isolation and characterization of *eceriferum* (*cer*) mutants induced by T-DNA insertions in *Arabidopsis thaliana*. *Genome* 36: 610-618; Marton L, Hrouda M, Pecsvaradi A, Czako M (1994) T-DNA-insert-independent mutations induced in transformed plant cells during *Agrobacterium* co-cultivation. *Transgenic Res* 3: 317-325.

[24] Wang G, et al (1996) Poplar (*Populus nigra* L.) plants transformed with a *Bacillus thuringiensis* toxin gene: insecticidal activity and genomic analysis. *Transgenic Res* 5: 289-301.

exhibited genomic changes when analysed. RFLP analysis indicated that, on average, the transformation procedure produced roughly on the order of 1000s of changes per genome. RAPD analysis of transformed plants, parent genotype controls and 4 additional poplar species demonstrated that the number of DNA polymorphisms in some of the transformed plants was similar in magnitude to the number of DNA polymorphsims found in an entirely distinct poplar species.

43. Genomic changes in 10 transgenic rice plants transformed via *Agrobacterium*-mediated transformation of callus were examined[25]. Using RAPD analysis they found 9 polymorphic bands out of 119 bands amplified in the 10 transgenic genomes. Using AFLP analysis, they found 19 polymorphic bands out of 288 bands analysed in the 10 transgenic genomes. There were no polymorphic bands in the 10 seed-derived non-transformed control plants.

Particle bombardment

44. The magnitude of genomic change in rice plants transformed via particle bombardment of immature embryos or electroporation of embryogenic callus was examined by analysing 12 transgenic T_3 plants transformed via particle bombardment and 15 transgenic T_0 plants transformed via cell electroporation[26]. Using RAPD analysis, no polymorphisms were found among the 252-261 bands amplified from any of the transformed plant genomes. Using AFLP analysis, a total of 12 polymorphic bands were found out of the 1711 total bands amplified from the transgenic genomes produced via particle bombardment. Six polymorphic bands out of 639 were seen in the 15 transgenic genomes produced via cell electroporation. The combined data from AFLP, RAMP and AFRP analysis suggests that transformation via particle bombardment or cell electroporation generated, on average, hundreds of changes per transformed plant genome.

45. Chromosomal aberrations in transgenic oats under two different tissue culture regimens were examined[27]. The authors state that: “Of the plants from 48 independent transgenic lines examined, plants from only 20 lines (42%) were karyotypically normal (2n=6x=42) without detectable chromosomal aberrations; plants from 28 lines (58%) had chromosomal variation, i.e. aneuploids and structural changes. No significant difference in cytological aberration was observed between the two different culturing systems used for transformation. In contrast, non-transgenic plants, regenerated from tissues comparable in age and culture media to that used for transgenic tissues, had a much lower percentage of karyotypic abnormality (0-14%).” The authors go on to say that that their methodology only permits quantification of "*gross changes in chromosomal integrity"* and that it is *"also likely that other less visible changes in chromosomal fidelity occur e.g. mutation, methylation polymorphism".*

46. Particle bombardment may have other hazards. When a locus generated by particle bombardment was sequenced it and discovered it contained chromosomal DNA from *E. coli*, presumably resulting from DNA impurities

[25] Labra M, et al (2001) Genomic changes in transgenic rice (*Oryza sativa* L.) plants produced by infecting calli with *Agrobacterium tumefaciens*. *Plant Cell Rep* **20**: 325-330.

[26] Arencibia A, et al (1998) Molecular analysis of the genome of transgenic rice (*Oryza sativa* L.) plants produced via particle bombardment or intact cell electroporation. *Mol Breeding* 4: 99-109.

[27] Choi H, G Lemaux P and Cho M. (2001) High frequency of cytogenetic aberration in transgenic oat (Avena sativa L.) plants. *Plant Sci* 160: 763-772

attached to the bombarded particles[28]. So few particle bombarded loci have been sequenced to date that this single report may indicate a significant phenomenon.

Intact cell electroporation or protoplast transformation

47. Analysis of 5 transgenic sugarcane plants, transformed via cell electroporation of embryogenic calli, using AFLP and RAMP techniques revealed a total of 51 polymorphic DNA bands out of 1237 analysed[29]. It was estimated that 814 Kbp of genomic sequence had been examined. Extrapolated to the entire genome, this represents, depending on estimates of total genome size, 100s to 1000s of genomic alterations per regenerated plant.

48. Analysis of transgenic rice produced via protoplast transformation using RAPD analysis showed 2-4% of the bands analysed were polymorphic between transformed plants and untransformed control plants[30].

49. The papers discussed above indicate that on average a minimum of 100s to 1000s of genomic changes are present in the genome of each transformed plant and that between 1% and 5% of the analysed sequences show polymorphisms. This body of work is clear and consistent and is clearly inconsistent with the view expressed (section 4.5, pages 56-57) that "there are no firm general results" of these studies and when the summary points out that GM plant breeding "presents special challenges", these should be spelled out fully.

Importance of backcrossing

50. There is another very important consideration in this context - both traditional and modern plant breeding programmes make extensive use of crossing and backcrossing to remove the trait of interest from its genetic background. The effect of crossing or backcrossing is to remove randomly created mutations and introduced genetic variation resulting from wide crosses, mutagenesis and other plant breeding techniques (such as tissue culture) from the genome of a crop variety before it is released. Thus much of the risk arising from random genetic mutations and other procedures is removed. In comparison, some GM crop varieties released commercially appear to have never been backcrossed. These include all transgenic varieties of potato and papaya. Other varieties appear to have been crossed minimally. Thus, many or all of the random genetic changes introduced by tissue culture and transformation are retained in the final variety.

51. All of this is not to say that one cannot find in certain places non-GM varieties which are well-known and have been derived in part from either induced polyploidy, wide crosses or induced mutation. It is to state that this is entirely a different proposition to having GM crop staples whose entire genome has passed through tissue culture and transformation without having been backcrossed significantly (significantly means 6-8 backcrosses) or even at all.

52. Importantly, we do not agree that mutagenesis, tissue culture and wide crosses are widely used to the extent claimed in section 4.2.1 paragraph 3. The reference (section 4.2.1, page 50), to the IAEA website supports our contention. The 1750

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[28] Ulker B, Weissinger AK, Spiker S (2002) *E. coli* chromosomal DNA in a transgenic locus created by microprojectile bombardment in tobacco. *Transgenic Res* 11: 311-313.

[29] Arencibia AD, et al (1999) Somaclonal variation in insect-resistant transgenic sugarcane (*Saccharum* hybrid) plants produced by cell electroporation. *Transgenic Res* **8**: 349-360.

[30] Bao PH, et al (1996) Evidence for genomic changes in transgenic rice (*Oryza sativa* L.) recovered from protoplasts. *Transgen Res* **5**: 97-103.

varieties (it includes non-food crops and ornamentals) listed on the website represent a tiny fraction of the plant varieties introduced worldwide since the 1960s (the period quoted). Of the references listed for the other breeding methods used, all, including Hayward et al 1995; Smartt and Symonds 1993 and Gept 2002 suggest that each has made only a modest contribution to plant breeding programmes. For example, most tomatoes contain a gene for *Fusarium* resistance from a closely related wild species. One explicitly states that although hopes were once high the actual contribution that these various methods have made to breeding programmes has not been as high as had been hoped (Smartt and Symonds 1993).

Other General Concerns:

53. Section 4.1 paragraph 2, line 1 states (and repeated section 4.4, line 1): **"***The current and widely accepted view within the biological research and plant breeding community is that there are important parallels between non-GM and GM plant breeding although in certain respects GM breeding techniques differ significantly, and that the methods of evaluation of GM crops for food, feed and the environment currently carried out within the European regulatory framework, are generally robust if consistently applied and should be effective*."

54. The assertion that this is a current and widely accepted view is not supported by any reference or survey.

55. As has been noted elsewhere, the Science Review has failed to assess the potential for alternatives. Where genetics (rather than, say, soil fertility or water availability) is a rate limiting factor in crop performance, marker assisted breeding (MAB) is a powerful and more acceptable way forward. MAB makes use of our ever increasing knowledge of genome structure (gene maps, QTLs, RFLPs, AFLPs, etc) in connection with specific traits. Although briefly mentioned [page 51, paragraph 3], the comparative advantages of MAB over GM are not highlighted including that MAB allows the far more rapid selection of desired traits from natural sexual reproductive crosses; MAB preserves normal gene order and regulation through the use of natural sexual reproductive processes; MAB allows selection for complex genetic traits such as drought resistance and salt tolerance which have multiple gene functions at their basis and that are extremely difficult or currently impossible to achieve through GM; MAB does not result in the release of GMOs into the environment or their entry into the food chain, which makes it generally acceptable to the public.

56. Furthermore, the following quotes illustrate how many see greater potential in MAB than genetic modification.

- *"The truth is that wheat priced at just over £50/t or even £60/t isn't sustainable for anyone... our thinking needs to be focussed downstream at our markets, innovatively and laterally...[to] give us a worthwhile competitive advantage.... The possibilities are as endless as they are exciting and they are achievable with existing technologies. Within the wheat plant we have a vast reservoir of genes. We also have the advanced analytical equipment necessary to pinpoint the molecular characteristics we need. And the marker-assisted systems to reliably build these characteristics into high output varieties through conventional plant breeding.... Our real challenge today is to work closely with the food industry and interest groups****...."*** Jeff Cox, general manager for Monsanto Northern Europe, Farmers Weekly (UK), 30 Aug 2002.

- *"Perhaps the greatest potential of biotechnologies does not come from GMOs but from genetic markers, genomics and proteomics which can complement conventional breeding strategies and enhance their efficiency".* Louise O Fresco, Assistant Director of Agriculture of the Food and Agriculture Organisation of the United Nations EU Discussion Forum 'Towards Sustainable Agriculture for Developing Countries: Options from Life Sciences and Biotechnologies', Brussels, 30-31 January 2003.

Chapter 5: The safety of food and animal feed derived from GM crops

Main findings:

- There are serious failings of approach that lead to an overly optimistic assessment of the ability to determine the safety of GM foods and complacency as to the potential for adverse effects.
- The chapter fails to make clear that there may be large differences between what is theoretically possible in GM food safety assessment, what could be achieved in the future, and what is *actually done* as part of the regulatory process.
- No attempt has been made to assess the quality and scope of the supporting dossiers for GM foods nor any analysis of regulatory decisions made to determine the quality of GM food safety assessment.
- Evidence exists that shows that *in practice* the theoretical possibilities are not followed and as a result the chapter gives an unrealistic analysis of the safety of GM foods in the food chain.

Regulatory practice

57. The lack of analysis of current practice means that the report presents an impression of GM food regulation and safety assessment in which best practice is always followed. For example, Section 5.2 states that four potential sources of toxicity and nutritional content "should be checked systematically in the case of each new GM crop" (p 64). However, there is no comparison between the desired theoretical assessments outlined and what is done in practice. A recent analysis of eleven EU application dossiers, conducted by the Austrian government[31], sets out a disturbing comparison between the theory outlined in the report and actual practice in the European Union:
    - The Austrian researchers noted that "*toxicological tests were carried out rather sporadically*", as opposed to being routinely conducted as suggested by the Science Review Panel's report.
    - The Science Review states that "testing the composition of the new crop, food or feed in its entirety in feeding studies" provides "a double safety check" (p65) and elsewhere it is stated that such testing "is done by undertaking typically a sub-chronic 90 day rat feeding study" (p69). The implication of the report is that such testing is standard procedure, yet the Austrian analysis of EU applications concluded "*data on the toxicity of the whole [genetically modified plant] are not provided in any dossier*" .

[31]Spok A, Hofer H, Valenta R, Kienzl-Plochberger K, Lehner P & Gaugitsch H (2002) *Toxikologie und allergologie von GVO-produkten: Empfehlungen zur Standardisierung der Sicherheitsbewwerung von gentechnisch veranderten Pflanzen auf Basis der Richtlinie 90/220/EWG (2001/18/EG)* Federal Environment Agency Monographien Band 109 Wien, Austria.

- The Science Review rightly states that "if the new gene product or endogenous plant metabolites were not as intended they could potentially lead to toxic, allergic or antinutritional effects". The Austrian report notes that, in reality, "*potentially toxic effects resulting as a secondary effect from the gene insertion are not considered in any case*".

58. The implication in the Science Review that GM foods are assessed using best practice approaches based on sound scientific analysis is entirely contradicted by the Austrian government's analysis which concludes that, in practice, GM foods "*are very often declared as being safe just by assumption based reasoning. Furthermore these assumptions are sometimes not easily or not at all verifiable*".

59. The failure of the Science Review to examine what happens in practice also means that the significance of the qualifying statements is not made clear. For example, in Section 5.2.2 it is stated that "the efficacy of testing depends on protocol compliance and the quality of the programme design" (p 65). In the absence of any analysis of the practice of GM food safety assessment, this reads as a sensible qualification to a theoretical discussion about approaches to GM food safety assessment. That this is crucial to the real world risk posed to consumers from the current generation of GM foods is only made clear in the context of actual practice. For example, the Austrian analysis of EU application dossiers concluded that most of the toxicological studies conducted had not met even basic scientific standards, such as Good Laboratory Practice.

60. Similarly, when considering the potential for unintended effects of gene insertion (p70), the Science Review argues that analyses for compositional, phenotypic, agronomic, nutritional and toxicological equivalence are sufficient to rule out any unintended consequences of genetic modification. This appears to be based on best practice guidelines as no actual examples are given of GM foods which have been subjected to such analysis. Yet again, the Austrian examination of actual EU applications concluded that "*the parameters chosen in composition analysis are however, not comprehensive enough to justify substantial equivalence and/or detect probable unintended secondary effects*". In fact, the Austrian report found that in every case there were significant differences between the GM and conventional counterpart, but that these differences were not investigated further. They concluded, "*on the ground of information given and data shown, substantial equivalence often cannot be verified*".

61. The risks posed by novel allergens in GM foods are also miscast largely because it is implied that the regulatory process will always be able to detect them. So, for example, it is suggested that the likelihood is "very low" that an allergen would not be picked up in regulatory screening (p79), and that if the 'shock' scenario discussed in the economic strand of the GM dialogue occurred, "all safeguards would have failed" (p 81). Yet this is contradicted even within the report, as it clearly states that there is wide disagreement in the scientific community about the utility of tests to predict allergenicity. The discussion also suggests that the current decision tree approach is uncontroversial, and that "the main science-related issues about allergenicity relate to the level of confidence in the practical testing regime" (p81). Yet at an international scientific workshop on the key issues in assessing the allergenicity of GM foods (published in June 2003), which included representatives of industry and regulatory authorities, it was noted that "*the group agreed that no realistic strategy had been proposed to protect the general population, including sensitive populations. Overall the procedures represented within the individual steps in the decision tree need to be better*

validated"[32]. This meeting of specialists in human allergies contradicts the impression presented in the Science Review.

62. Statements are made about the thoroughness of the regulatory system which do not appear to be reflected in practice. For example, it is stated that in the case of a novel protein containing amino acid sequence homology greater than 28% (6 consecutive amino acids) with known allergenic proteins "the regulatory authorities would not approve the development of the GM crop" (p 82). In fact, using sequence alignment, a recent study found that 22 out of 33 transgenic food proteins examined displayed identical stretches of at least six contiguous amino acids with allergenic proteins[33]. While it is probable using this strict criterion that a large number of these were false positives, the researchers went on to plot predicted antigenicity of the transgenic protein and make comparisons with previously described linear IgE-binding epitopes. Using this more detailed approach they concluded that three transgenic proteins, glyphosate oxidoreductase (GOX), papya ringspot virus coat protein and acetolactate synthase warrant further clinical investigation. GOX has been used in the development of some Roundup Ready crops as the enzyme increases the rate of glyphosate degredation. For example, a partial (inactive) GOX gene is contained in Monsanto's GM glyphosate tolerant fodder beet line A5/15 for which a marketing application has been made in Europe and which was part of the farm scale evaluations in the UK.

63. Similarly, while the FAO/WHO decision tree for the assessment of allergenicity is set out, its application in practice is not examined and, therefore, a false impression is created. In fact, a recent examination of applications to the EU found that the decision tree was not followed correctly in many cases and that, despite the requirements within for testing with serum screens or animal models, "*no direct testing of potentially allergenic properties was carried out*"[34]. The Science Review report rightly points out that analysis of pepsin resistance provides only some indication of potential allergenicity but because it did not include an analysis of actual practice, no mention is made of the fact that this is the test that has been predominantly relied upon, often exclusively, in assessments of GM foods to date.

64. The practice of GM safety assessment is greatly different to the theory as laid out in the Science Review report. Some examination of the regulatory procedure was included, but apparently without any critical analysis and it is surprising that this should not have been picked up by the Panel, particularly as members of regulatory committees were included. Unfortunately, the result is that the Science Review gives a misleading and overly optimistic assessment of GM food safety because the Review failed to examine actual practice as opposed to best practice. That this was not included in the initial framing of the Panel's deliberations is a serious oversight, which needs to be addressed before any of the report's claims about the risks posed to consumers by GM foods can be taken seriously.

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[32] Germolec DR, Kimber I, Goldman L, Selgrade MJ (2003) Key Issues for the assessment of the allergenic potential of genetically modified foods: Breakout Group Reports *Environmental Health Perspectives* 111(8) 1131-1139

[33] Kleter GA and AACM Peijnenburg (2002) Screening of transgenic proteins expressed in transgenic food crops for the presence of short amino acid sequences identical to potential IgE-binding linear epitopes of allergens. *BMC Structural Biology* 2(8) www.biomedcentral.com/1472-6807/2/8

[34] Jank B & Haslberger AG. (2003) Improved evaluation of potential allergens in GM food *TRENDS in Biotechnology* Vol.21 No.6 249-250

Evidence of safe consumption

65. The checklist provided in the methodology of the Science Review correctly highlights that the quality of evidence used in support of different arguments should be considered. Yet in section 5.2.6 it is stated that "The fact that GM food crops have now been grown on over 230 millions cumulative hectares worldwide over the past seven years (ISAAA, 2003) does provide evidence for the lack of harmful human health effects from the consumption of GM food products." While the report itself does goes on to state that it is "only evidence for the lack of more serious and readily observable health effects", it is questionable whether even this is accurate. In fact, reporting of health effects of the type that could be expected from GM foods may well be insufficient to easily detect even serious impacts. In a recently published review of procedures in the United States it was noted that in the case of allergic reactions, no record is kept of the number of emergency admissions and the potential allergen is rarely identified, even repeat visits for reactions to well-known allergens are not counted toward any national surveillance[35]. Thus there is no means of establishing even the current status of food related illness, let alone any changes in occurrence or new reactions to foodstuffs.

66. The lack of labeling further complicates the matter as most US citizens have very limited means of establishing whether or not they are eating GM foods and so self-reporting of health impacts is likely to be very unusual. The only known cases of self-reporting of GM food related illness came after the widely publicized Starlink contamination, and even in that case, when vast resources were applied to the effects of a single GM food, it has been concluded that "*intensive epidemiologic investigation and laboratory test development by federal investigators was not sufficient to determine whether individual allergic reactions were associated with the inadvertent release of a genetically modified protein into the human food chain*"[36]. There is, in fact, no reliable evidence for safe consumption of GM foods, primarily because there has not been even the most basic attempt at monitoring in the United States and, as even serious ill health may be going undetected, it would seem inconsistent with the Panel's checklist to use this as support for the position that safe consumption is occurring.

Benefits for developing countries

67. It is disappointing that the SRP report repeats the misconception that GM foods will provide a solution to malnutrition in developing countries (p 76). This position has been widely criticized by a number of major development NGOs, as well as officials from developing countries, as being an overly simplistic application of a proposed technological solution to an extremely complex social and economic problem. Put simply, the causes of malnutrition are almost entirely due to social and economic causes such as poverty, access to land and resources, the development of export-led cropping at the expense of domestic food production, war and so forth. The misconception that GM crops can really do anything to address malnutrition from such causes was largely discounted in the Strategy Unit's economic review of GM crops, and so it is disappointing that the Panel should have continued to put forward this discredited position. The likelihood of golden rice and golden mustard making any real impact on worldwide malnutrition is very low when the technology is set against the societal context.

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[35] Bernstein, JA, Bernstein L, Bucchini L, Goldman LR, Hamilton RG, Lehrer S, Rubin C and Sampson HA, 2003. Clinical and laboratory investigation of allergy to genetically modified foods. *Environmental health perspectives* 111(8) pp 1114-1121

[36] *Ibid*

5.4 The fate of transgenic DNA

Main points

- Chapter 5.4 is written from the assumption that there is little risk and very few remaining uncertainties about horizontal gene transfer (HGT) in the GI-tract and it does not give a balanced review and assessment of the current knowledge.
- Many issues are not considered or inadequately addressed including the use of the CaMV promoter; problems which may be faced by people with malfunctioning of their intestinal tracts; antibiotic resistance genes and the differences in intestinal tracts between species.

68. The summary of Chapter 5.4. does not reflect the real concerns outlined in the paper and fails to consider the limitations of knowledge and is not an accurate representation of text. Whilst the main text states that homology provides an "efficient" mechanism for gene transfer, the summery only state "a mechanism". The summary should also mention that there has been only one study of humans eating GM derived food and that this showed the survival and transfer of the transgene to gut bacteria. And this one study indicates that DNA survival and transfer can occur to a high degree in people with unhealthy GI-tracts (here ileostomists). The summary should refer to recombination and homology: "At a very low frequency, maintenance as a result of an 'illegitimate' recombination event is possible."

69. On page 90 (Background) it states: "*The potential for transgenic DNA to be transferred from GM material following its consumption is a recognised hazard that is addressed during the safety evaluation process.*" No indication is given as to how the safety evaluation process evaluates these safety concerns or addresses them. There should be an examination of how adequate such processes are in practice as well as in theory.

70. On p.93, "….it is clear that DNA detection in areas of the body beyond the gastro-intestinal tract lumen is a natural phenomenon that does not impact on human health." When this phenomenon has not been further studied – and implications have not been researched.

71. Assumptions are used repeatedly without inquiry into their basis and 'no evidence' is brought into play to downplay risks. E.g. p.94 "*There is no evidence that transgenic DNA behaves differently from other DNA in the diet both with respect to its survival and its fate following consumption in GM plant material*." Since "fate" includes whether a DNA sequence transfers horizontally – and there are clear and documented differences between plant DNA and transgenes, the quoted statement is contested but there has been very little research undertaken.

72. Chapter 5.4 implies that HGT is well understood. However, little is known about the environmental conditions or circumstances under which organisms acquire DNA sequences, or their requirements for sequence homology. This should be more clearly documented in section 5.6.6.

73. There is no mention or review of the use of the CaMV 35S promoter as a promoter potentially equally active in plants, bacteria, yeast or possible higher animals. Lewin (2000) recommended that no promoter should be used in transgenes for plants that can be active in other organisms. Though her paper is cited, her conclusions aren't.

74. There is no mention, discussion or review of the use of transgenes derived from higher organisms which can be transferred to microorganisms and potentially expressed for the first time as introns are removed.

75. There is no recognition or discussion of the different capacity of the gastro-intestinal tract to degrade DNA or remove its biological activity with respect to individuals who do not have a healthy GI-tract.

76. The paper does not consider HGT and its potential consequences to species other than humans and some farm animals. Fish are not mentioned, nor the impact on birds, small mammals, insects, pollinators etc. which could potentially ingest transgenic plants.

77. The paper fails to underline that different animal species have different GI-tracts or GI-tract conditions. Thus feeding studies or *in vitro* model studies can only be regarded as representative for that particular species under the given condition and cannot be extrapolated to any other species.

78. There is no discussion or even mention of HGT, its risks and potential consequences with regards to yeast and other non-bacterial microorganisms that reside or can reside in the GI-tract.

79. The issue of antibiotic resistance marker genes (ARMs) is not satisfactory dealt with and only gives one side of the argument. For example, the review fails to mention that much of the antibiotic resistance conferred by transgenes is to antibiotics used in human and veterinary medicine and the use of these marker genes brings a risk of increasing antibiotic resistance in disease causing organisms. For example, ampicillin remains a very widely used antibiotic and is still the antibiotic of choice for *Enterococcus* and *Listeria monocytogenes*[37]. Neomycin is still used in veterinary medicine and although its use is restricted in humans, is used for cases of drug resistant TB.

5.4.4 – Is there general scientific agreement?

80. This section is somewhat biased and does not reflect general understanding. The consensus is rather that there has been very little research into HGT within the GI-tract of humans and animals and until further evidence is found and further research undertaken, no clear statements can be made. Further there is general agreement that the use of ARMs should be phased out – though there is no agreement on impact or risk of the use or ARMS.

5.4.8. Where there is important scientific uncertainty, what is the way forward

81. There is clear and not “limited” scientific uncertainty re HGT in GI tract. It is not ‘confidence’ that should be sought, rather increased knowledge.

[37] Stellungnahme der ZKBS zur Biologischen Sicherheit von Antibiotika-Resisten, Oct 18, 2001. Robert Koch Institut. http://www.rki.de/GENTEC/ZKBS/ALLGSTELL/99/ANTIBIOTIKA.HTM]

Chapter 6 Environmental impacts of GM crops

6.2 – Invasiveness/persistence of GM plants

Main points:

- There is an excessive reliance on a single study – the PROSAMO experiment – which gives a misleading impression of the extent of knowledge.
- A lack of critical evaluation of limitations of PROSAMO study means its importance is raised inappropriately.
- Pleiotrophic effects may affect invasiveness but are not considered – only intended changes are discussed.
- The PROSAMO findings may not, in any case, be applicable to crops in FSEs as the GM crops studied contained different GM constructs.
- More uncertainty exists in our understanding of invasiveness than is acknowledged.

82. In this section, there is an excessive reliance on the PROSAMO experiment and publications arising from it and a lack of proper consideration of the wider literature. As a result, the review supports the Crop Model and rejects the Alien Model Species (which predicts a 1 in a 1,000 risk of invasiveness) by relying on a sample of 4 GMOs with no associated statistical analysis to support the conclusion. To find out if GM does or does not fit the alien model you are likely to need several thousand distinct plant strains and either a long period or a sufficiently large scale to overcome the lag aspect. PROSAMO is, therefore, largely irrelevant in this respect. The Science Review should acknowledge this and correct the summary and content of Chapter 6.

83. There is no critical evaluation of the limits of the PROSAMO experiment, its design and associated publications cited (Crawley et al., 1991; 2001). For example, although the experiments were innovative an on a larger scale than previously, they had some limitations which needed more attention in the review as they have implications for the conclusions which can be drawn:

- Annuals are typically, and for obvious reasons, plants of disturbed ground and, therefore, they would be expected to become problems primarily in disturbed habitats such as arable fields. The PROSAMO experiment looked at the crops in undisturbed habitats so were looking for a most improbable short-term result and naturally failed to find it.
- Selection pressure through the application of a herbicide as might occur on field margins or other disturbed ground was not included.
- Sugar beet and maize seed were only sown in one year and OSR only in the first three years of the ten year experiment, so year on year recruitment was not examined.
- As a commentary on the paper stated: *..history tells us that an ultimately successful invader might fail miserably, or barely persist for decades, before exhibiting explosive population growth*[38]. In addition, the relatively high levels of error even with these experiments have been noted (Parker & Kareiva, 1996).

84. The assumption underlying the section is that the introduced trait determines invasiveness – there is no acknowledgement of the potential for unanticipated changes which might affect persistence/invasiveness in either direction. This is in contrast with other parts of the Science Review e.g. 6.3.2 para 4 last sentence

[38] Kareiva, P. (1993) Transgenic plants on trial. Nature 363: 580-581.

'*These examples of "pleiotrophic effects" might not pose significant risks to the environment, but they illustrate the importance of considering the whole plant as well as the expected effects of the transgene"*. This should also be reflected in the discussion of invasiveness. Recent work[39] has shown how genetic modification for insect resistance affected biochemical pathways in the plant associated with natural resistance and which may in turn affect ecological persistence – possibly negatively in this case but which needs to be determined for each transformation event.

85. One conclusion in this section is that the findings of the PROSAMO experiment show that '*the GM plants studied were no more invasive or more persistent in semi-natural habitats'*. However, because the PROSAMO plants are not the same GM lines that are available for commercial growing in Europe now (the papers detailing the experimental findings do not give details of the constructs used, but the herbicide tolerant oilseed rape is reported to have a kanamycin resistance gene which is not in the FSE OSR), more caution is needed in any conclusions about the potential invasiveness of these lines - pleiotrophic effects that influence persistence may (or may not) be present. Therefore, more uncertainty needs to be acknowledged.

86. In section 6.2.6 on uncertainties, it needs to be noted that plants with only very small genetic differences can behave very differently in terms of invasiveness and in ways which are not understood[40]. Therefore, it is not correct to say we do not have an exact understanding, as if our knowledge was almost complete, the uncertainties and ignorance are considerable. There are also considerable practical difficulties (because of time, cost and scale) in designing experiments to provide the data that might be considered acceptable (Parker & Kareiva, 1996) that should be referred to here.

87. The invasive potential of annuals is excessively downplayed in the section. For example, two wild oats *Avena fatua* and *A sterilis* and common field-speedwell *Veronica persica*, are all costly agricultural weeds. *Avena fatua* is usually thought to be derived from cultivated oats. Wild cabbage is now considered naturalised and is thought to have originated from feral populations (see Section 7.3.2; Preston, 2002). This dimension needs to be more fully considered in this section.

6.3 Toxicity to wildlife

Main points

- The executive summary is not consistent with the section summary.
- The difficulties of understanding complex ecological impacts of potential toxins in GM plants are well covered in the main text.
- That the ecological role of Bt is unknown is not mentioned although it makes the uncertainties involved even greater.
- The summary refers to changes in other non-target pests but does not review the evidence.
- Internationally agreed standards are inappropriate because of national and regional differences in ecosystem structure and function.

[39] Birch et al (2002) (The effect of genetic transformation for pest resistance on foliar solanidine-based glycoalkaloids of potato (*Solanum tuberosum*) Annals of Applied Biology 140: 143-149
[40] Willamson, M. 1996. Biological Invasions. Chapman & Hall

88. It is unclear why the executive summary does not replicate that of the section itself. The first paragraph in the executive summary includes data relating to pesticide use which are not in the full section. A 'no evidence' argument is introduced in relation to soil ecosystem impacts.

89. This section does review all the major literature concerning the potential toxicity to wildlife of GM crops. However, it does not explore some of the limitations on assessing specificity of toxins – inevitably a restricted range of species is tested and some uncertainty remains whether all the appropriate species have been evaluated. In this context, it is important to note that Event 176 Bt maize was given commercial approval before its toxicity to Monarch butterflies was fully investigated illustrating the inevitable shortcomings of risk assessments. This is another instance where practice in risk assessment may not match the theoretical possibilities.

90. Our ignorance of the ecological role of Bt toxin in *Bacillus thuringiensis* should be referred to as it underlines how difficult it is to predict impacts on soil ecosystems in particular – see Box 4.1 *The mysterious ecological role of Bt toxins* (page 162) in National Academy of Sciences (2002) Environmental impacts of transgenic plants: the scope and adequacy of regulation. National Academy Press. One recommendation should be for further research to understand the natural ecology of Bt.

91. Not all pests of cotton or maize are affected by Bt – sucking pests, which vary according to the region of the world where the crop is being grown, are not affected for example. Stink bugs in the USA and jassids in South Africa are examples of such insects and where populations may be changing as a result of the use of Bt crops. This may have ecological or agronomic impacts that should be considered[41].

92. Section 6.3.4 refers to the lack of internationally agreed standards. The extent to which such standards would be appropriate needs exploring considering the diversity of ecosystems across not only the world but also individual countries/regions.

6.4 Development of resistance

Main points

- Uncertainties surrounding the geographical use of certain constructs in many species and the emergence of resistance are not addressed.
- The mistaken impression is given that experience with GM virus resistant crops is extensive.
- The importance of farmer behaviour in relation to resistance management is not discussed.
- The ability of GM to introduce entirely new forms of resistance not possible through conventional breeding and the consequences this brings is not addressed.

[41] See e.g Bachelor, J.S. (2001) Managing insects on cotton. Chapter 11 in *2001 North Carolina Cotton Production Guide.* http://ipm.ncsu.edu/Production_Guides/Cotton/chptr11.pdf; Joubert, G.D. *et al* (2001) South African experience with Bt cotton. International Cotton Advisory Committee. Technical Seminar of the 60th Plenary Meeting, Victoria Falls, Zimbabwe, 16-21 September 2001. http://www.icac.org/icac/cotton_info/tis/biotech/documents/techsem/SAexperience_tis01.pdf

93. One factor which may affect the emergence of resistance, and which is unique to GM, is the extent to which certain gene constructs may be used across a range of different crop species, across the world. For example, herbicide tolerance (to glyphosate based on the EPSPS gene) has been introduced into a whole array of different crops to be used globally. Similarly, the use of Bt genes as a basis of lepidopteran resistance in cotton has taken place on a worldwide basis. This introduces new areas of uncertainty as to how this will affect the emergence of resistance because of the unprecedented scale and extent of exposure.

94. Section 6.4.3, in reference to viral disease states that '*several GM food crops expressing virus-derived sequences as novel resistance transgenes have been deployed commercially in the US, China and Africa*'. No reference is given for this or details. Virus resistant papaya are grown in Hawaii and some virus resistant squash and potatoes in the USA (although neither are thought to be in commercial production now). There are no commercially grown virus resistant food crops in China and Africa that we are aware of. Box 7.1 refers only to experimental work and this should be made clear.

95. One of the main challenges with resistance management is whether farmers will be able or willing to comply with the systems put in place. As the review states this may not be feasible in countries where there are many small farms. However, there is evidence that even in the USA, up to 33% of farmers do not comply[42]. Not only should this be considered here but it also raises important questions for future research into what systems would be practicable and how they should be best enforced.

96. Section 6.4.5 asks whether the issue is unique to GM? As it says, there are conventionally introduced forms of resistance in a wide range of crops. However, as the following illustrates, there are also important differences about the source of the genes which may have important consequences and which should be included here: '*When the transgenes derive from viruses, they are substantially different from current 'natural' resistance/tolerance traits in terms of context and ubiquity. Their presence introduces a substantially new dimension into the dynamics of plant/virus coevolution, even though virus-derived nucleic acids are normal constituents of natural plant populations where they undoubtedly contributed to the evolution of viruses, Hitherto, virus evolution has been affected by multiple infections constrained, at least in part, by the serendipitous behaviour of vectors. There is a risk that the spread of virus-derived transgenes will eliminate this element of chance as the presence of viral nucleic acid becomes uncoupled from vector behaviour"[43].*

97. The reference Fitt (2001) (bottom of page 141) is misunderstood. He does not claim resistance is emerging in aphids etc (which are not sensitive to Bt in any case) but that the use of Bt and decline in lepidopteran pests may lead to an increase in Bt insensitive pests which could make management more complex. Therefore the following paragraph contests something which has not been stated.

98. The reference Conway (2003) on page 144 is not cited in the reference list.

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[42] (Coghlan A. (2001) Almost a third of US farmers broke rules for planting GM maize last year. *New Scientist*, 5 February 2001).

[43] Cooper, J.I. & Raybould, A.F. (1997) Transgenes for stress tolerance: consequences for weed evolution. The 1997 Brighton Crop Protection Conference – Weeds pp 265-272.

6.5 New weed control strategies offered by GM herbicide tolerant crops

Main points

- This is a comprehensive and detailed account of our stage of knowledge

99. This section gives a comprehensive review of the issues surrounding weed control and GM HT crops. There are only a few minor points of clarification. Page 150, para 4, glyphosate is a systemic herbicide, not a contact herbicide. Page 152, para 2, it is glufosinate that is being used alongside atrazine in GM HT maize in the US

6.6 Horizon scanning

Main points

- This section is too superficial and does not consider the realities
- There is no mention of alternatives or comparative analysis
- This section illustrates clearly the unique abilities GM has to transform plants but this is denied

100. Almost inevitably perhaps, this section suffers from being too superficial and variable in its content and is of questionable value to the review. In particular, it does not examine the extent to which it will be possible to achieve the desired changes both in technical and economic terms. It does not explore, for example, the difficulties which have been encountered in modifying biochemical pathways in plants to produce oils as industrial feedstocks. Neither does it consider in any depth the extent to which it will be feasible to use biofuels to replace existing energy sources. For a more critical evaluation of some of these issues see: Murphy, D.J. (2002) Biotechnology and the improvement of oil crops – genes, dreams and realities. Pytochemistry Reviews 1: 67-77.

101. We also note the comments of the BTO on the Science Review[44] who have considered in depth the literature cited in section 6.6.4 and concluded that much has little in the way of hard evidence on ecological impacts and is often anecdotal. We agree with their comment that there needs to be a much more critical evaluation of the quality of the literature.

102. Most strikingly, despite emphasising the need to make comparative evaluations with other options as a part of a precautionary approach (Box 3.1), this section fails to do that. It is only by including such comparisons that some sensible and critical evaluation can be brought to bear.

103. The reference Wipff & Fricker (2000) cited on page 171 is incorrect - this could not be found in the journal BioScience.

[44] http://www.gmsciencedebate.org.uk/report/comment/pdf/0011.pdf

6.7 Changes in agricultural practice

Main points

- This section is very weak and lacks serious analysis.
- We agree that modern, intensive farming has had major negative impacts on the environment. What is now needed is approaches which will reasonably reliably deliver substantial improvement in the environmental impact of agriculture. Further negative impacts or only uncertain or limited positive impacts are not acceptable.
- A range of other impacts of GM crops needs to be considered including the effects on farming practices and choice of non-GM farmers.

104. This section is very weak and lacks any depth in its analysis. It fails to really consider the wider context of agriculture and becomes little more that a different construction of the equally weak section on horizon scanning. The scenarios are entirely based on the technology and fail to consider other changes or alternatives.

105. The representation of the range of views and evidence is very weak and partial. For example, any analysis must consider the following:

- we consider it is much more possible not “equally possible” (p 178) that GM crops may reduce biodiversity. Greater weed/pest control is a key attraction of the current generation of GM crops and, as mentioned in the following paragraph, HT crops can encourage the uptake of minimum-tillage which depends on herbicides, so increasing herbicide use. Bt crops may have impacts on non-target species as discussed elsewhere in the report.
- there are reasons why GM crops could reduce, not increase, the diversity and use of crop rotations (p179). The effect of HT volunteers are discouraging GM crops farmers from rotating in Canada.
- GM crops, some evidence suggests, will bring economic disbenefits rather than benefits.
- Bt corn in Spain has not been universally successful. Studies in 1998, 1999 and 2000 show that, contrary to the industry claims, Bt corn produces below average yields (1-9.6% less than average), which is much less than the highest yielding varieties (8-20% less). Also, it takes longer to mature and the data suggests it may suffer more second generation corn borer attacks than non-Bt varieties. [45]
- HT and insect resistant GM crops could bring certain agronomic convenience benefits for those adopting them. However, overall, and increasingly in the longer term, farmers are likely to be much inconvenienced.
- The need to control HT volunteers in ensuring years, deal with weed resistance, and implemented Bt refuges will be new problems.
- The requirements for segregation, traceability, labelling and co-existence measures will all bring totally new problems for farmers growing GM crops, requiring many new farming practices.
- GM crops may undermine the choice of farmers, both those growing and those not growing GM crops. The risks of gene flow may restrict the crops that can be grown. GM crops will undermine the availability of organic farming as an option (see below). The choice of farm saved seed may be removed. The North American experience shows that following on from the introduction of GM crops, there is also a fall off in the choice of non-GM seed varieties on the market as the

[45] The Impact of GM corn in Spain, by FoE and Greenpeace, 26 August 2003.

companies invest more in developing new GM varieties and promoting the sales of GM over non-GM varieties to seed distributors.

- Weed or insect resistance to agro-chemicals also used by non-GM farmers such as glyphosate and Bt sprays would undermine not only the GM crops but the general use of those products in agriculture and lead to more toxic or less effective replacements. The development of Bt resistance would undermine organic farming.

6.8 Limitations of science

Main points

- The title of the section should be 'Limitations of science in environmental impact assessment' – it does not consider health or agronomic impacts.
- The summary (and much of the section) does not reflect the intended subject of the section and makes excessive claims for the FSEs.
- The limitations of the case-by-case approach are not discussed.
- The discussion on the limitations of environmental modelling and experimentation is limited and partial.
- Evidence that small scale experiments do not always predict large scale impacts has not been included.

106. The scope of this section is restricted to environmental impacts and the title should be modified to make this clear.

107. The summary does not even address the subject matter. It makes incorrect statements which discredit the other sections of the review where considerable effort has been made to explain the uncertainties involved. For example, the final paragraph of the summary says '*The FSEs <u>will</u> show <u>any</u> environmental implications specific to GM herbicide tolerant crops*' (emphasis added). This is simply not true. No place is given in the summary to other findings in the section such as: ..*in many cases, such as soil ecology, invertebrate ecology and breeding ecology of birds there is not yet the scientific background to use this approach [prediction] with confidence (*page 191) or '*Predictions are dependent upon understanding the underlying processes and determining sufficiently accurate parameters. There are, however, examples in which insufficient understanding of the process confounded predictions)* (page 190). These important limitations in the science should be given more prominence in the summary.

108. We would expect a discussion of the limitations of GM science and the environment to begin with some of the overarching issues and we suggest that a new section to cover these issues is introduced. These would include:

- the practical constraints on experimental design (including financial);
- the problems of extrapolating from small to large and commercial scale;
- the difficulties of detecting small incremental changes which become significant only over long time periods;
- lack of knowledge of complex ecological interactions;
- different types of error and;
- the constraints on modelling when there is a lack of data and assumptions have to be made about environmental systems which may or may not be correct.

109. Overall, the section is extremely partial, in favour of GM and in considering the indirect impacts of GM HT crops as posing the only significant risk. The last 2

paragraphs of page 191 are an extreme example of this. Given the issues identified elsewhere in the review this does not seem to be substantiated.

110. One of the main conclusions of the science review is that a case-by-case approach has to be taken to the assessment of GM crops. Whilst this may superficially appear the most sensible approach, there are limitations which need to be understood and which should have been critically evaluated in this section. Areas where regulatory systems based on a case-by-case risk assessment are inadequate include:
- An exclusion of comparative assessments so that it is not possible to make choices between different options.
- An inability to address generic questions about, say, the overall impacts of HT crops on patterns of herbicide use.
- That the emphasis on each individual GM crop is likely to lead to a lack of data on interactions between GMOs.
- That cumulative impacts are not adequately dealt with.
- Excessive emphasis on the introduced trait diverts attention from pleiotrophic impacts.

111. Gene flow is one area where there are data illustrating the clear difficulties in scaling up from small-scale field trials to larger scale or commercial activities, yet these are not discussed here. For example, Squire *et al* (1999) have shown how large pollen sources, such as fields, have different pollen distribution characteristics than that predicted from small-scale experiments. Very recently, it has been shown that small-scale studies can considerably underestimate of the hybridisation between *Brassica napus* and its relative, *B. rapa* [46].

112. There are some strange contradictions in this section. For example, the last sentence of para 4, page 189 states '*If there were dramatic affects [sic] then it seems probable that these would have been detected'*. Yet the last sentence of the following paragraph says: *'In the future there are also likely to be suites of changes, so that determining any causal role for GM crops is likely to be difficult unless there is a detailed programme to examine this specifically'.*

113. Parker & Kareiva (1996) is referred to on page 188, paragraph 5. However, it does not include the main subject matter of the paper, namely the difficulties and constraints on examining fitness.

Chapter 7 Gene Flow, Detection and Impact of GM Crops

7.2 Gene flow between crop varieties

Main points

- The section recognises the difficulties the inevitability of gene flow and the many uncertainties in our knowledge about gene flow.
- In its interpretation of the data, the section does not recognise that consumer choice of GM free food, the needs of the organic sector, market and farming realities are important issues in the consideration of gene flow.

[46] Wilkinson, M.J. *et al* (2003) Hybridisation between *Brassica napus* and *B.rapa* on a national scale in the United Kingdom. Science express 9th October. www.sciencexpress.org/9October2003/Page1/10.1126/science.1088200)

- Certain key data and examples are missing.
- The effects of multiplication over generations, increases in the area of GM crops, and feral populations are not properly addressed.
- Some statements are incorrect (in particular with regards GM crops in Spain).

Recognising the problems

114. There are many important issues identified in the report which have implications for co-existence :

- The complete genetic isolation of most crops on a commercial scale is not practical for the foreseeable future: gene flow between crop varieties is inevitable.
- There is little evidence on how the different factors (seed purity, cross pollination, volunteers, gene stacking etc.) will combine, which makes prediction of gene flow difficult.
- The distance that pollen travels depends on a variety of factors including climatic conditions and topography.
- Gene flow between crop varieties has generally not been studied on a farm or regional scale.
- GM volunteers can act as a reservoir of transgenes and lead to changes in farming practice that can affect biodiversity.
- The tools for sampling, detecting and quantifying GM presence must be in place at an international level if gene containment within specific thresholds is to be possible.
- Monitoring gene flow will be important in ensuring the co-existence measures are working and in refining current predictions.
- Minimising the dispersal of genes through seed is essential.
- Non-food GM crops must be separated from food varieties.

Consumer choice and organic farming – GM free crops

115. Although the report recognises these important issues, surprisingly, for a review intended to address public concerns, this section does not consider this in the context of public concerns: the extent to which, if at all, consumers will still have a choice of GM free, UK produced food and whether UK organic farmers will be able to produce uncontaminated crops. If consumers want to avoid GMOs, they generally want to avoid all of them, not just 99%. The section occasionally suggests that co-existence is necessary for consumer choice but gives a very restricted interpretation of consumer choice which needs revision. The inclusion of the political statement by Franz Fischler is inappropriate - particularly without consideration of information on what consumers mean by choice. The organic sector requires GM contamination in organic crops to be below the limit of detection (currently 0.1%) to meet its principles and certification and market requirements – this needs to be acknowledged and addressed.

116. Most of the analysis and comment of this section should, therefore, have been directed at considering gene flow to non-GM crops at zero or limit of detection levels (0.1%), instead of 1%. The text also often refers to the ability to contain gene flow to “low levels”. This is not specified but appears to be of the order of 0.5-1% which we do not consider a reasonable basis for the review.

Market realities

117. In addition, all the major supermarkets and food manufacturers in Europe have non-GM food policies, which they are operating with limits on GM presence of a maximum of 1% and in many cases 0.1%. Similar policies for animal feed are being implemented. This is in response to consumer demands and to the

legal labelling thresholds. Supermarkets say that they must use testing limits below the legal limits to avoid unintentional cases of contamination being above the legal limits in individual cases, because all food lots are tested and that there are variations from lot to lot. Because of the risk of admixture during transport, handling and processing between the farm gate and the retailer, the Science Review should also recognise that *farm gate* levels of GM presence often need to be lower than retail requirements.

Farming realities

118. This section seems highly naïve with respect to the realities of farming. The implementation of co-existence measures is likely to be very problematic in practice. Even if adequate measures could be designed, inevitable breaches of implementation which will mean a constant risk to non-GM farmers. The recent SCIMAC survey of the highly aware and supportive farmers engaged in the Farm-scale Trials (April 2003), revealed 13 potential instances of non-compliance just through telephone checks. Even in cases where communications between farmers are good, measures such as rotation planning will interfere with the need of farmers, especially organic farmers, to plan rotations years in advance but to still have the flexibility to change their plans depending on climatic and market conditions. Farming is also a messy business - there is geographical and seasonal variability, and individual skills are highly variable - so the average rates of gene flow established in experimental conditions will only apply to a limited number of cases in reality. Major allowances need to be built in if co-existence systems for meeting specific thresholds are to be reliable and this dimension needs further consideration.

119. The practical problems for farmers monitoring the contamination of their crops has also not been considered. For example, those growing for non-GM markets including organic farmers may need to identify any contaminated parts of their fields before harvesting machinery is used. For standing crops, they will not have the same ability and resources as those further up the food chain to mix grain and make up large samples sizes, to have accurate on site testing facilities, or the ability to wait for results to come back from laboratories.

The wider importance of gene flow

120. Gene flow is significant for reasons other than determining whether co-existence is feasible for a variety of other reasons which also need to be included in the review:

- *Consumer choice* - the text should be amended to recognise that gene flow *per se* is important. The second paragraph states that 'whether gene flow matters will depend on its consequences' but this is then contradicted several pages later in 7.2.3 by the acknowledgement that a group of people consider that any amount of gene flow is unacceptable.
- *Protecting agricultural genetic resources* – it is a concern that the Mexican maize contamination incident is not considered.
- *Safety* – it is clearly wrong to dismiss the relevance of gene flow to safety. On p. 204, the review says that GM crops posing a hazard should not be released and so gene flow does not represent exposure to risk. This does not recognise the uncertainties and assumptions in the GMO safety assessment processes, and that monitoring of the post-release impacts is a legal requirement to confirm the assumptions. Also, gene flow from unapproved varieties or from non-food crops can be hazardous. The StarLink maize contamination case should be considered: although unapproved for food use, over half the national US supply of maize was contaminated. The

independent scientific advisory committee on the incident concluded that there was a "medium probability" that the maize could cause the allergic reactions.[47] Having controls on gene flow in place is also vital for damage control and limitation, should a hazard emerge.

- *Farmer choice and market orientation of agriculture* – farmers need the freedom to respond to the market and to policy goals such as the expansion of organic farming and meeting consumer demands, which means being able to produce GM free crops. As well as the impacts of farm level gene flow, farmer choice will be reduced by the inevitable restriction in non-GM seed sources, as has been the experience in North America, due to the problems of maintaining purity of both certified and Farm Saved Seed (FSS) non-GM lines. The analysis does not adequately recognise the extent of FSS: some 70% of UK farmers use FFS (p.59, Strategy Unit economic report, "Field Work") and at least 40% of oilseed rape is FSS. FSS will be affected not just by GM crops grown by those farmers, as stated, but also by GM crops grown in the surrounding area.
- *Legal reasons* - such as identifying the source of gene flow and for determining liability in cases of contamination; and for patent infringement claims by the biotechnology companies (see Seeds of Doubt, Soil Association, September 2002).
- *Agricultural trade* – one of the main impacts of GM crops in North America, has been the dramatic loss of major export markets to Europe and Asia for soya and maize, due to the lack of segregation (see Seeds of Doubt, Soil Association).
- *Protecting the organic farming sector* – this is neglected in the study and important examples should be included: the loss of the organic oilseed rape sector in the main organic farming province in Canada, Saskatchewan (see Seeds of Doubt, Soil Association), and the reduced organic maize production in the Navarra region of Spain, both resulting from the threat of contamination from GM crops (26 August 2003 report, The Impact of GM corn in Spain, by FoE and Greenpeace). This is important for environmental reasons - organic farming has many proven environmental benefits; the Government is committed to its expansion; and it has a high level of public support.
- *Protecting the national seed industry* – the Advanta rape contamination incident should be noted as an example of how inadequate gene flow containment can damage the seed industry. The Canadian Government inquiry found that despite separation distances of over 800m, three-quarters of the final seed lots were contaminated at up to 2.6%[48]. As a consequence, the company relocated its operation from west to east Canada and New Zealand as the only way to avoid a repetition of the problem.
- *Avoiding product recalls* – there have been many documented cases of seed recalls and food products recalls, involving significant economic cost and disruption to many actors in the food chain (Seeds of Doubt, Soil Association).
- *Minimising herbicide tolerant (HT) volunteers*.

Important omissions

121. The report is obscure about the separation distances it is assuming would be used. On p. 200, it states that the proposed recommendations from the Ingram (2000) report "form part of the basis for current assessments of gene flow", but

[47] Scientific Advisory Panel, *SAP Report no. 2000-06*, 1 December 2001 www.epa.gov/scipoly/sap/
[48] See FoE press release, 4 May 2002, www.foe.co.uk/pubsinfo/infoteam/pressrel/2002

these are not stated nor are any other distances clearly proposed. This is even though the report states several times that 'separation distances for specific thresholds' can be predicted for most crops and regularly refers to a 1% threshold or "low levels" as the assumed objective. Similarly, the report must be specific about which crops it is referring to when commenting on the levels of gene flow, instead of just vaguely referring to 'some crops' (eg. bottom of p. 198 "For some crops, maintaining thresholds …may be relatively straight forward…. However, in other cases it may be difficult")..

122. In section 7.2.3, 'To what extent does gene flow occur', there is a section on the limited experiences of controlling gene flow and another on scientific studies, but there is no reference to the several spectacular failures in controlling gene flow and preventing negative consequences in areas where GM crops have been grown. The report should describe the details and relevance of:
- The StarLink maize contamination case.
- The Advanta rape contamination case.
- The extent and problems of HT volunteers in Canada – this is mentioned but the highly serious level of the issue is not made clear, for example that HT rape has now become of Canada's top ten agricultural weeds and led to a return to the use of older, more toxic herbicides.
- The destruction of the organic oilseed rape sector in Saskatchewan due to GM rape.
- The serious problems with Bt maize in Spain – very worryingly, the report presents the Spanish case as an example of the implementation of strategies for co-existence and suggests the maize has been successful (p.209). No reference is cited for this. Until recently there were no independent data, only industry reports. The report should include the findings of a NGO report in August 2003 that listed many problems: the lack of any gene flow containment measures; the fact that the GM crop locations are not being made public despite demands by organic farming organisations; that a couple of organic farmers have had their crops contaminated in one region and lost the organic certification of their crops; that organic farmers in that region have now drawn back from growing maize because of the uncontrollable risk; that the Bt varieties have been if anything lower yielding and possibly even more attacked by the target pest (the corn borer) than non GM varieties, contrary to industry marketing claims and indicating that insect resistance may either already have or be developing.

123. The report does not address the key policy issue, and one of grave public concern, of whether GM presence in non-GM crops can be stabilised or will increase over time due to multiplication over generations and increases in the area of GM crops.

124. The report should mention that the key concern of the EU Scientific Committee on Plants in its opinion on thresholds for GM seeds in conventional seeds[49] was that the legal labelling limits were only be achievable in the best growing conditions and with best practice, and would be increasingly difficult to achieve as GM production increases, so that "in due course, the 1% threshold may have to be revised".

[49] SCIENTIFIC COMMITTEE ON PLANTS: SCP/GMO-SEED-CONT/002-FINAL 13 March 2001 Opinion of the Scientific Committee on Plants concerning the adventitious presence of GM seeds in conventional seeds. (Opinion adopted by the Committee on 7 March 2001)

Misleading and inconsistent general conclusions

125. If GM crops are to be commercialised, knowledge of the control and thus predictability of gene flow is crucial. It is clear from the evidence cited that gene flow is currently and probably intrinsically unpredictable. This needs to be made clear and prominent, including in the Executive Summary. This is because there is little knowledge on how the different factors will combine (seed contamination, cross pollination, volunteers etc.) and because some of these factors are inherently variable over time and space (pollen dispersal varies with climatic conditions and topography) – these are stated but the conclusion with respect to controlling gene flow is not. In addition, the variable aspects of the realities of farming, in terms of the consistency of the implementation of co-existence measures, need to be factored in.

126. Currently, almost the opposite impression of predictability is given by the report: the statement that separation distances for specific thresholds can now be predicted is repeated several times as is the statement that 'low levels' of gene flow can be maintained for most varieties. These must be incorrect and should be amended: if the contribution of other factors is unknown, then the necessary separation distances and their practical feasibility cannot be reliability predicted for real agricultural conditions. In addition, much of the relevant research for farm and regional-scale gene flow is missing. This is important because pollen concentrations at agricultural scales are very much higher and have different characteristics to experimental scale plots (Timmons *et al*, 1995). However, this crucial point is not made clear until the end in 7.2.6 (Are there gaps in knowledge?).

127. The report needs to recognise that different studies have revealed very different levels of gene flow over similar distances. Rather than trying to suggest that one set of data can be selected over the rest, as it currently does by referring to the predictability of the distances and the use of specific distances, it would be much more appropriate to recognise that the range of findings confirms the variability and unpredictability of gene flow in real-life situations, and that reliance on only 'average' findings would result in many failures in gene flow containment. If one set of data is selected, the criteria for the selection and rejection of the other studies would have to be explained.

128. The mentions of separation distances need to reflect better the considerable disagreement over the distances needed for specific thresholds and over what the thresholds should be. There is not consensus, for example, on the statement on that separation distances have been effective and used to successfully minimise gene flow (p.198). We are not aware for any rigorous research on this subject.

Over-optimistic about oilseed rape

129. The report is seriously over-optimistic about the potential for controlling gene flow from oilseed rape and very misleading. Rather than suggesting that further research might produce more hopeful information, it should state openly that from the large amount of the evidence it is clear that containment is impossible or at best excessively costly, and refer to the JRC report from the European Environment Agency; the NPRU pollen report[50], the DEFRA Research Report No.

[50] Tru, R. & Emberlin, J. (2000) Pollen dispersal in the crops maize, oilseed rape, potatoes, sugar and wheat – evidence from publications. A report for the Soil Association from the National Pollen Research Institute.

12 – Feral Oilseed Rape Populations (February 1999); the Canadian experience; and the recent DEFRA report just added to their website [51].

130. Further important and relevant information that should be included:

- the JIC report detailing that cross pollination has been found at 4km (not a maximum of 3km as in the review); that feral populations can act as a source of contamination; and that the additional costs to farmers of changing farming practice even to meet a 1% threshold would be 10-41% .
- The NPRU report reviewed the evidence which included findings that a 5% cross pollination rate occurred at 4km using male sterile plants as traps (52 traps were used over 70 square km, Thompson *et al*) and that a 0.8% cross-pollination rate occurred at 2.5km (Timmons *et al*, 1995) also using male sterile plants. The report must note that a substantial proportion of oilseed rape in the UK is now varietal associations and about 80% of these are male sterile plants[52].
- The Canadian experience that gene stacking occurs very readily with HT rape - it was found at all 11 potential locations investigated by Agriculture Canada (part of the Department of Agriculture and Agri-food), and 3 genes can be stacked in only two years according to field trials by the University of Idaho (Seeds of Doubt, Soil Association).
- The latest DEFRA research on the contribution of GM rape volunteers to gene flow, states that only "the most rigorous field management" of feral/volunteer plants, would make GM levels fall below 1% in five years.
- Dr Sweet's statement on 16 April at a meeting in Aberystwyth that "We do have to accept the fact that once GM oil seed rape is commercialised it will be everywhere and is inevitable, because conventional rape is everywhere".

7.3 Gene flow from GM crops to agricultural weeds and wild relatives

Main points

- A relatively comprehensive review of the literature and reference to different views which acknowledges the inevitability of gene flow to wild relatives.
- Needs to include new data on likely frequency of gene flow to wild relatives in the UK.

131. This section does have an extensive review of the literature and acknowledges areas where knowledge is uncertain. It refers to the spectrum of opinions and attempts to address them.

132. The recent paper showing that the levels of hybridsation between oilseed rape and wild turnip are higher than previously thought needs to be included[53]. Reinforcing the findings of this study, in determining the likelihood of gene introgression into wild species, recent modelling studies indicate that, in cotton and brassicas, the most critical assumptions relate to pollen dispersal[54].

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[51] The potential for oilseed rape feral (volunteer) weeds to cause impurities in later oilseed rape crops, DEFRA, report of DEFRA research project RG0114

[52] EU Scientific Committee on Plants, opinion on adventitious presence of GM seed in conventional seed, March 2001.

[53] Wilkinson, M.J. *et al* (2003) Hybridisation between *Brassica napus* and *B.rapa* on a national scale in the United Kingdom. Science express 9th October. www.sciencexpress.org/9October2003/Page1/10.1126/science.1088200)

[54] Thompson, C.J. *et al* (2003) Model-based analysis of the likelihood of gene introgression from genetically modified crops into wild relatives. *Ecological Modelling* 162:199-209.

Therefore, the behaviour of pollen should form an important dimension of research. However, the authors of the modelling paper concluded that '*..the general conclusion is that even very small amounts of dispersing pollen may lead to surprisingly high risks of unwanted events, when the events are integrated over reasonable time frames and when the account for some of the kinds of uncertainties that are present in all ecological systems'.*

133. The section concludes that gene flow to wild relatives is not an issue for wheat. While the extent is very unlikely to match that for oil seed rape, there is evidence that hybridisation can occur here. In northern Europe, there are two wild relatives that wheat have been crossed with wheat in controlled breeding studies - sea barley (*Hordeum marinum*. Huds.) and bearded wheat grass (*Elymus caninus* L.). In a study of English and Austrian populations of these plants, one bearded wheat grass plant found in Sounthy Wood near Peterborough, showed evidence of wheat specific genes, demonstrating that natural hybridsation and introgression of wheat genes into wheat grass is possible[55].

7.5 Can genetic material in GM plants transfer to viruses?

Main points

- This is a seriously flawed discussion of the risks arising from the recombination of GM transgenes with viruses.
- A combination of poor scholarship and confused reasoning combine to exaggerate estimates of safety and to diminish or ignore concerns. The result is not therefore a fair-minded estimate of the risks of GM crops containing viral transgenes and it fails to make the case that new and recombinant viruses will not prove hazardous.
- Important risks associated with the use of virus transgenes are ignored.
- It relies upon confused reasoning and discredited arguments.
- The implications of important experiments are misconstrued and peer-reviewed literature misinterpreted.
- It accepts uncritically a poorly-designed study as evidence for crucial assertions and gives priority to anecdotal evidence in preference to the results of well-accepted methods.
- The general views of plant virologists as shown in a DETR 1999 survey are not properly represented.
- Conclusions are made which are entirely unsupported by evidence.

Risks ignored

134. Chapter 7.5 ignores entirely one of the main risk issues involved in the use plant virus-derived transgenes. This is the potential for virus-derived transgenes to make crop plants more susceptible to other viral diseases rather than the one being protected against. Numerous reports show that expression of a viral protein in a transgenic plant can make that plant susceptible to viruses which are related or unrelated to the virus from which the transgene came. Almost all types of virus protein have been shown to have this ability to complement other viruses: viral coat proteins[56]; viral movement proteins [57]; viral replicase proteins[58] ; viral

[55] Guadagnuolo, R., Savova-Bianchi, D., Keller-Senften. & Felber, F. (2001) Search for evidence of introgression of wheat (*Triticum aestivum* L.) traits into sea barley (*Hordeum marinum* s.str. Huds.) and bearded wheatgrass (*Elymus caninus* L.) in central and northern Europe, using isozymes, RAPD and microsatellite markers. Theoretical and Applied Genetics 103: 191-196.

[56] E.g Taliansky, M. E., and Garcia-Arenal, F. (1995). Role of cucumovirus capsid protein in long-distance movement within the infected plant. *J Virol* 69(2), 916-22; Briddon, R. W., Pinner, M. S.,

proteins involved in overcoming host defences[59] and various miscellaneous viral proteins[60]. More than a hundred references attest to this fact. Plants transgenically expressing plant viral proteins can even support infection by insect viruses[61]. Thus such GM crops may be especially susceptible to new infectious viral diseases.

135. The potential for expression of viral capsid proteins to transfer viruses to new hosts by allowing them to be transported by unfamiliar vectors is only addressed briefly and inadequately It assumes, without presenting evidence, that since no immediate genetic change occurs, that no risk ensues (p242 para2).

136. Whether the use of an extremely poorly understood viral resistance mechanism presents a risk for food safety addresses is considered only briefly and inadequately. Viral resistance derived from transgenes appears to arise as a result of the targeting of the transgene and the virus by a powerful degradative biochemical pathway whose specificity and stability is a matter of speculation. The use of gene silencing in this way raises profound questions which are ignored here and elsewhere in the report. The review accepts the use of gene silencing because it is a natural phenomenon whilst ignoring that gene silencing is a sequence-specific phenomenon. Just because gene silencing is used by the plant itself, it does not follow that gene silencing based on sequence homologies chosen for it will be safe. Other plant breeding techniques certainly could not introduce such sequence homologies.

137. The risk of recombination with non-homologous viruses is ignored and this position justified on two grounds. The first is a tautology (7.5.3 p241 para 6 sentence 2 starting with "And"). The second reason is an assertion that contradicts numerous observations of non-homologous viral RNA recombination[62]

Stanley, J., and Markham, P. G. (1990). Geminivirus coat protein gene replacement alters insect specificity. *Virology* 177(1), 85-94.

[57] E.g Cooper, B., et al. (1995). A defective movement protein of TMV in transgenic plants confers resistance to multiple viruses whereas the functional analog increases susceptibility. *Virology* 206(1), 307-13; Ziegler-Graff, V., Guilford, P. J., and Baulcombe, D. C. (1991). Tobacco rattle virus RNA-1 29K gene product potentiates viral movement and also affects symptom induction in tobacco. *Virology* 182(1)**,** 145-55.

[58] Siegel, R. W., Adkins, S., and Kao, C. C. (1997). Sequence-specific recognition of a subgenomic RNA promoter by a viral RNA polymerase. *Proc Natl Acad Sci U S A* 94(21), 11238-43; Teycheney, P. Y., et al. (2000). Synthesis of (-)-strand RNA from the 3' untranslated region of plant viral genomes expressed in transgenic plants upon infection with related viruses. *J Gen Virol* 81(4)**,** 1121-6.

[59] Pruss, G., et al (1997). Plant viral synergism: the potyviral genome encodes a broad-range pathogenicity enhancer that transactivates replication of heterologous viruses. *Plant Cell* 9(6), 859-68; Sonoda, S., et al. (2000). The helper component-proteinase of sweet potato feathery mottle virus facilitates systemic spread of potato virus X in Ipomoea nil. *Phytopathology* 90, 944-950.

[60] Agranovsky, A.A. et al. (1998). Beet yellows closterovirus HSP70-like protein mediates the cell-to-cell movement of a potexvirus transport-deficient mutant and a hordeivirus-based chimeric virus. *J Gen Virol* 79 (Pt 4), 889-95; Sunter, G., Sunter, J. L., and Bisaro, D. M. (2001). Plants expressing tomato golden mosaic virus AL2 or beet curly top virus L2 transgenes show enhanced susceptibility to infection by DNA and RNA viruses. *Virology* 285(1), 59-70.

[61] Dasgupta, R., Garcia, B. H., 2nd, and Goodman, R. M. (2001). Systemic spread of an RNA insect virus in plants expressing plant viral movement protein genes. *Proc Natl Acad Sci U S A* 98(9)**,** 4910-5.

[62] Banner, L. R., and Lai, M. M. (1991). Random nature of coronavirus RNA recombination in the absence of selection pressure. *Virology* 185(1), 441-5. Lai, M. M. (1992). RNA recombination in animal and plant viruses. *Microbiol Rev* 56(1), 61-79; White, K. A., and Morris, T. J. (1994). Nonhomologous RNA recombination in tombusviruses: generation and evolution of defective interfering RNAs by stepwise deletions. *J Virol* 68(1), 14-24.

and which would not anyway constitute sufficient reason to ignore recombination with distinct viruses.

Transgene-virus recombination

138. Chapter 7.5 is confused and muddled about its main subject - estimating the risks from recombination between viruses and viral transgenes. It sometimes uses the term 'recombination' in the specific and narrow molecular sense (as in the joining together of two nucleic acid molecules (DNA or RNA) e.g. in the summary-para 3 or Greene and Allison 1994[63]) and sometimes in the wider sense as the process that allows the evolution of new viruses (e.g. in the summary para 4 or Thomas et al 1998). This lack of clarity becomes the basis for exceedingly important confusion as the chapter proceeds to equate experiments addressing one sort of recombination with experiments addressing the other.

139. Eleven reports (e.g. Greene and Allison 1994) detailing virus-transgene recombination with various plant viruses have been published. These reports demonstrate that virus recombination with a transgene is a common outcome of infection by a homologous or near-homologous virus. It is common even when the invading virus is substantially disabled - such that it can only invade a few cells of the host. Chapter 7.5 misconstrues a technical necessity of these experiments (that the recombining virus was disabled) as invalidating their implications for the prevalence of recombination in field scale situations with non-disabled viruses (in both the summary 7.5.1 and 7.5.3 p241 paras 2-4).

140. By conflating the two types of recombination, Chapter 7.5 attempts (in the summary, 7.5.1 and 7.5.3 and elsewhere) to contrast the evidence demonstrating the occurrence of recombination by the narrow definition (e.g. Greene and Allison 1994) with evidence against recombination by the wider definition (using Thomas et al 1998). This sets up an apparent and needless conflict between the two and postulates that the multiple and undisputed (except in Chapter 7.5!) demonstrations that viruses frequently recombine with transgenes is trumped by a single experimental report of failure to observe new recombinant viruses in the field (Thomas et al 1998[64]), plus some anecdotal evidence.

141. The experimental evidence (Thomas et al 1998) for failure to observe new viruses in the field is crucial to the argument of Chapter 7.5 (it is quoted in the summary and three more times in the text). However, it derives *entirely* from a study that, as well as being a negative result, represents a catastrophic failure of the peer-review process (Thomas et al 1988). The limitations of this study are set out in the box below. It is not an appropriate basis on which to reach a conclusion of no or little risk.

142. Although two papers are cited, the remaining 'evidence' quoted[65] is entirely anecdotal. It is anecdotal because these two papers do not report *any* experimental evidence or monitoring data to support the claims of Chapter 7.5. These papers do not even make any statement that could be construed as suggesting that no recombinants have arisen.

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[63] Greene, A. E., and Allison, R. F. (1994). Recombination between viral RNA and transgenic plant transcripts. *Science* 263(5152)**,** 1423-5.

[64] Thomas, P., et al. (1998). A search for evidence of virus/transgene interactions in potatoes transformed with potato leafroll virus replicase and coat protein genes. *Mol. Breeding* **4,** 407-417

[65] Ferreira, S. A., et al. (2002). Virus coat protein transgenic papaya provides practical control of papaya ringspot virus in Hawaii. *Plant Dis.* 86, 101-105. Gonsalves, D. (2002). Control of papaya ringspot virus in papaya: a case study. *Ann. Rev. Phytopathol.* 36**,** 415-437.

143. As a fall back position, Chapter 7.5 asserts (summary 7.5.1) that new viruses are unlikely to arise by recombination because they will be out-competed by other viruses which have been honed by "millennia of evolution"(7.5.1). This general argument has a dubious theoretical pedigree and few contemporary supporters. In any case it is specifically contradicted by the evidence: that new plant and human viruses do constantly evolve (e.g. SARS, HIV) and that viruses introduced into new areas often prosper despite locally-adapted competition.

144. Chapter 7.5 (summary 7.5.1) misrepresents the potential to control any new viruses that may arise as a result of recombination. It implies that methods generally exist to control new virus outbreaks when for only a handful of known viruses is this true.

145. The maximum number of infected viruses found in a single plant[66] is 5 not 11, additionally this number does not originate in a peer-reviewed experiment but from a personal observation of one of the authors (Falk). No information is provided as to how this number was obtained.

146. Under range of views (7.5.3) states that the views of Latham and Steinbrecher (2003) form a minority. Interestingly, in the only ever survey of professional virologists, 14/34 respondents cited transcapsidation and 16/34 cited recombination as being potential hazards[67]. This is a very substantial minority. Given the opportunity of quantifying these risks, only 2 of the above and 5/34 rated the risks as being inconsequential. These views are especially significant considering that the terms of the questionnaire were that respondents comment only on their own experiments (or system) and not those of others.

147. Chapter 7.5 claims that New Leaf virus-resistant potatoes were grown commercially. This is not true (Gonsalves 2002). Absence of evidence in this case is clearly not evidence of absence (section 7.5.3 p242). Nor is quoting Thomas et al (1998) correct at this point as their experiments were not with the New Leaf lines which were approved, this mistake is repeated on p246 para 2).

148. 7.5.3 (p241 para 6) argues that transgenes targeted by gene silencing "clearly" show "greatly reduced" recombination. The relationship between silencing and recombination with a transgene has never been investigated and this conclusion is pure speculation.

[66] Falk, B. W., and Bruening, G. (1994). Will transgenic crops generate new viruses and new diseases? *Science* 263(5152)**,** 1395-6.
[67] Safety of plant viral inserts. Research report No.11 DETR 1999.

A critique of Thomas et al 1998[68]

A special place for Thomas et al (1998) is reserved in our response to Chapter 7.5 because Thomas et al is quoted four times including being one of only two papers quoted in the summary. Thomas et al is so extensively cited because it is said to support the contention that recombinant viruses are unlikely to arise as a consequence of the use of plants expressing viral transgenes.

However, Thomas et al (1998) is a negative result and therefore needs to have a reliable methodology if one is not to mistake lack of evidence with absence, in this case, of recombination. Unfortunately, Thomas et al's methodology is deeply flawed:

The authors test for recombination by asking whether the new viruses will acquire new properties and then searches for these new properties. Unfortunately, the properties for which the authors search are ones that a recombinant virus is unlikely to exhibit and, furthermore, they do not search very hard for them.

a) The authors look for recombination by examination for symptoms in transgenic potato plants that became infected by viruses. Is it reasonable to expect that recombination events would reveal themselves by affecting symptoms in the plant in which the recombination event occurred? The transgenic lines were inspected once or possibly twice only in the course of their lifetime (p410).

b) The authors look for viruses with different sedimentation characteristics, but only for recombinants between PLRV and the PLRV rep transgenes. No reason is given for why one would expect such recombinants to exhibit altered sedimentation, why one would expect a new virus to manifest itself in this way over the background of wild type virus, or whether the new virus would not be lost on transference to a new host (*D. tatula*). No indication is given of how many samples were tested, or what controls were used. Since virus symptoms of PLRV were reported on these transgenic plants presumably they were not resistant to PLRV. Perhaps this is because they were not expressing the transgene? This is a crucial point because mRNA expression from the transgene is a necessary precondition for recombination to occur with RNA viruses.

c) The authors looked for alterations in host range and symptoms of viruses in sap removed from transgenic plants showing symptoms of viruses other than PLRV. No indication is given that this technique is a sensitive test for recombinant viruses and there is no good reason to suppose that a new recombinant virus would manifest itself as having a changed host range or symptomatology against a background of wild type virus. The sensitivity of the test depends on how many indicator plants were used to test each sample of sap but this is not reported. Another major question mark concerns the donor transgene which comes from PLRV, a virus that is not sap transmissible. There is no reason to suppose that a new recombinant virus which acquired the coat protein or replicase of PLRV would possess this sap transmissibility. Again it is unclear which if any of the transgenic plants used were actually capable of expressing mRNA at the time they were infected.

[68] Thomas, P., et al (1998). A search for evidence of virus/transgene interactions in potatoes transformed with potato leafroll virus replicase and coat protein genes. *Mol. Breeding* 4**,** 407-417.

d) A similar experiment was performed by deliberately exposing “selected” transgenic lines to virus infection. The basis for this selection is not given. Again, similar points apply as in c) above.

There is also a more general point. Thomas et al examined recombination to create new viruses with transgenes derived from PLRV. Even if the methodology of Thomas et al had been well thought out and thoroughly performed, it would only apply to recombination with these two transgenes from PLRV.

No single negative result, even one much better than Thomas et al, should ever occupy a central place in this or any other risk review and it certainly should not be the very basis of a firm conclusion of lack of risk.