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- More on Terminator and Related Patents

Transcript

Witness Statement of Mae-Wan Ho

Chardon LL Hearing, Novotel, London, October 26, 2000

MAE WAN HO: My name is Mae Wan Ho. I obtained my Bachelor of Science degree in Biology in 1964, and my Ph. D. in Biochemistry in 1967 from Hong Kong University, and was Postdoctoral Fellow in Biochemical Genetics, in the University of California in San Diego from 1968 to 1972. During that time, I won a competitive Fellowship of the US National Genetics Foundation, which took me to London University in the United Kingdom, where I became Senior Research Fellow in Queen Elizabeth College.

I then became Lecturer in Genetics from 1976 and Reader in Biology from 1985 in the Open University. Since retiring early in June 2000, I remain Visiting Reader in Biology at the Open University, and I am also Visiting Professor of Biophysics in Catania University, Sicily.

My career so far spans more than 30 years in research and teaching in biochemistry, evolution, molecular genetics and biophysics. I have over 200 publications, including ten books.

MR ALESBURY: I have been given one of them by another party, not by you.

MAE WAN HO: Since 1994, I have been scientific advisor and spokesperson for the Third World Network, which is a non-Government organisation based in Penang, Malaysia. I have been their spokesperson on biotechnology, biosafety and related issues, and have produced many reports and papers on the subject for policy-makers and the general public, as well as articles for peer-reviewed scientific journals.

In 1999, I co-founded the Institute of Science in Society (ISIS) of which I am Director. I-SIS is a not-for-profit organisation, promoting socially and ecologically accountable science and the integration of science in society. I-SIS also represent a group of scientists around the world (currently 364 from some 40 countries) who have co-signed a World Scientists Statement and Open Letter to All Governments, calling for a moratorium on environmental releases of GMOs on grounds that they are unsafe, and to revoke and ban patents on life-forms and living processes, on grounds that they are unethical.

I just want to refer to this document here which I have called AP/1.

MR ALESBURY: No, you have to copy our numbering system; so it is BG/1A.

MAE WAN HO: This is a recent version of the letter. It is not the most up-to-date; that is where there are 345 scientists instead of what I have said.

What I would like to say is that the most up-to-date version is on the I-SIS website, the address of which is www.isis.org. It is at the bottom of the first page of BG/1A.

MR ALESBURY: It is also in your footnote 1.

Accepting that this is not the very latest version, do you want to point me to anything in particular in it?

MAE WAN HO: I shall be doing so in due course.

What I would like to do, first, is to reiterate I-SIS's written objections to placing Chardon LL on the National List, which are contained in our written submission. It was submitted in April.

The first is that the initial EU approval for Chardon LL is unlawful, according to EU's own regulations.

The second objection is that the data submitted by the company fail in important respects to satisfy international agreements on safety of GMOs already reached on the Biosafety Protocol and the Codex Alimentarius Commission of the World Health Organisation.

The third objection is that the transgenic insert contains hazardous DNA.

The fourth, the tests conducted by the company fail to address impacts on health and biodiversity.

Rather than repeat my written objections or our written objection here, I want to take this

opportunity to explain why GMOs are different, how they are made, why they are inherently unreliable and unsafe, as you have already heard from Caroline Clarke, and how current regulatory processes fail to protect health and biodiversity, using Chardon LL as a case study.

I shall say that--

MR ALESBURY: Really it is a mundane point, but a little point I want to get out of the way. When you made that reference to the previous written representations, you are there talking about those which were put in by I-SIS, not the Burnhams Group.

MAE WAN HO: No, not the Burnhams Group.

I am using the Chardon LL as a case study because, precisely as I said, the incompleteness of the data submitted by Aventis really forces us to look at what is available in the scientific literature, on transgenic crops and GMOs in general.

One of the major shortcomings of current regulatory systems is their fragmented state. It reflects the fragmented state of the science itself. Those busy exploiting the technology for biomedicine are unaware of what is happening in agriculture and *vice versa*. Many applications are not regulated because they fall between the scopes of different directives and regulatory bodies. Regulators pay lip-service to the precautionary principle which is enshrined in the International Biosafety Protocol under the United Nations Convention on Biological Diversity, negotiated in Montreal in January 2000, and to which the United Kingdom is a party.

In practice, however, they have been (our regulators, that is) adopting the anti-precautionary approach, and confusion abounds over how scientific evidence is to be used and interpreted.

Here, I introduce BG1/B, which is *I-SIS News*, issue number 6. I draw your attention, particularly, to the report on page 3, "Dangerous GM wastes, recycled as food, feed and fertiliser". It describes the situation in so-called contained use of genetically engineered micro-organisms. Then the one immediately following on the next page, "EU directive on deliberate release still inadequate", the title of which is self-explanatory.

On page 14 of this same document there is an excellent article by Dr Peter Saunders, Professor of Mathematics at Kings College, London. I have to declare an interest here in saying that it is excellent because he is my husband. It is on "Use and abuse of the precautionary principle", which I shall come back to later.

GMOs are a new departure from conventional selective breeding. The creation of genetically modified organisms (or GMOs) is a new departure from conventional selective breeding and introduces new hazards. This view is shared by many scientists, including those advising the United States and the UK Governments. Of course, going back to BG1/A, it goes without saying that all the 364 scientists who have, as of I think a week ago, signed our statement agreed with this position.

But I would like to draw your attention especially to page 6, paragraph 11, where it says:

> "Secret memoranda of US Food & Drug Administration reveal that they ignored the warnings of its own scientists that genetic engineering is a new departure and introduces new risks ."

The footnote for this item is:

> "Secret memoranda came to light as a result of a civil lawsuit spearheaded by a lawyer, Steven Drucker, against the US Food & Drug Administration, May 1998 (footnote 37)."

For details you can visit their website, which is also listed here.

The other point I want to stress is that the techniques and nature of artificial constructs (which I shall refer from now on as GM constructs) made are the same in all the applications of GMOs, whether in agriculture or in biomedicine, and so are the hazards involved.

Here, I would like to say that the current regulatory system does not take that into account, because there is the Department of Agriculture, Ministry of Agriculture, there is the Health & Safety Executive, dealing respectively with agriculture and with health.

Then you ask: "What will happen to crops that are in the pipelines, we are told, which are going to be genetically engineered to produce pharmaceuticals and also industrial chemicals; which ministry will they come under?" These are just some of the problems I am highlighting.

Conventional selective breeding is restricted to crossing varieties within a species of between closely related species with similar genetic make-up. That is because genetic barriers prevent reproduction between unrelated species and limit the exchange of genetic material between them.

GMOs are created in the laboratory by genetic engineering, and genetic engineering involves techniques that modify the genetic material directly. The genetic material, for those who do not know already, is the deoxyribonucleic acid, or DNA for short.

MR ALESBURY: Remember that the transcript writer is trying to take down the transcript directly from your speech, which of course you are diverging interestingly and usefully from the text a bit.

MAE WAN HO: I think it will be very boring to follow the text directly.

MR ALESBURY: I make no comment about that, but I am just making the point that it is helpful if you just proceed not at an excessively slow pace but at a measured pace; so that it can be taken down.

MAE WAN HO: I shall be measured in all respects.

I have here a transparency illustrating the structure of DNA, which is a long string made up of units. The string actually is double. It is called a double helix. It is like two pieces of electric flex wound around each other. The units are labelled A, T, G and C. Interestingly, A always pairs with T, G always pairs with C and, hence, it gives you a mechanism whereby

you can copy DNA or replicate it precisely. That is, in theory.

This A, T, G and C is repeated apparently at random for millions or billions of times. The exact sequences of these units matter, because they code for specific proteins and enzymes that make up the intricate structures of the organism and enable the organism to transform material and energy to grow, develop and do all the things that constitute being alive.

The totality of all the genetic material of an organism is its genome. For example, the human genome has more than three billion of these units. The genome, this genetic material, is organised in a specific way typical of a species, and is represented in every cell of the organism. They are organised into linear structures called chromosomes. The human genome, for example, has 23 pairs of chromosomes.

In making GMOs, genetic material from different sources are cut and recombined to make artificial GM constructs that are then transferred into the genomes of organisms. So, genes can be combined from widely disparate sources, and transferred between species that would never interbreed in nature.

So, for example, you used to have a children's joke, what do you get when you cross impossible things like a spider with a goat? You know it was a joke because these things are impossible. Now, this ceases to be a joke any more, and it has been done. The spiders silk gene has been put into a goat in order to make the poor goat, the female goat, produce spider silk in her milk.

In other words, the GM constructs are designed to overcome species barriers and to invade genomes. There is, thus, no limit to the new genes and new combinations of genes that are made in the laboratory, nor to the GMOs created, all of which may never have existed in billions of years of evolution.

What genetic materials are used in GM constructs and how are GMOs made? Most of the genes used in GM constructs originate from a wide variety of bacteria and viruses that cause diseases and other genetic parasites which spread drug and antibiotic resistance genes. A gene is never used by itself. It needs a start and a stop signal, a promoter in front and a terminator at the back.

This promoter, I will show this simple diagram. This transparency shows a unit GM construct, which consists of three parts; promoter, gene, terminator, in that order. Very often the three parts of the expression cassette -- this is called an expression cassette because, with this, the gene here can be expressed into protein, or to produce the protein product -- originate from different sources. The promoter is usually from a virus, which makes the gene overexpress at very high rates continuously to make lots of the protein or gene product. This is something that never happens in a healthy organism, and effectively puts the gene outside the normal metabolic control or regulation of the GM organism.

The most common promoter used in plants is from the Cauliflower Mosaic Virus, CaMV. It is a plant pathogen. The CaMV 35S promoter -- it is one of the promoters in the virus -- is in practically all GM crops already commercialised or undergoing field trials.

The gene *pat* coding for resistance to the herbicide glufosinate in Chardon LL is derived from the soil bacterium, *Streptomyces viridochromogenes*. It is joined to the CaMV 35S promoter and also the CaMV 35S terminator.

MR ALESBURY: I gather it came from soil samples in Cameroon or somewhere like that, the *pat* gene.

MAE WAN HO: Yes.

Apart from the expression cassette containing the genome of interest, in this case the herbicide resistance gene, it is necessary to have at least one other cassette containing an antibiotic resistance gene with its own promoter and terminator. This enables the genetic engineer to select for cells that have taken up the GM construct with the antibiotic. The antibiotic kills off all the other cells. Two or more expression cassettes are then linked or stacked in series in a typical GM construct.

Chardon LL has an expression cassette for *AmpR*, a gene coding for resistance to the antibiotic ampicillin. This gene belongs to the gut bacterium, *Escherichia coli*, or *E. coli* for short, although the gene is not actively expressed in the GM plant

For ease of handling and bulking up GM constructs, and for transferring the constructs into genomes, genetic engineers make a large variety of artificial gene carrier or vectors by combining parts of the most aggressive natural vectors -- and these are called viruses, plasmids and transposons.

MR ALESBURY: Can I just ask you something to do with the previous paragraph to that one, because I am quite interested in that. That is actually the first time this particular aspect has been explained by anyone who has been here.

This business about the reason why there is the cassette containing the antibiotic resistance gene as well -- which I have to say although a lot of people have mentioned that it has puzzled me until now why it was used, but you have explained.

I am just not quite clear. I understand this point that the gene is not actively expressed in the genetically modified plant.

MAE WAN HO: I shall come to that. I shall come to that very important point. You are very sharp. So there is a reason for that.

MR ALESBURY: How it cross-relates to the purpose for which it is used in establishing--

MAE WAN HO: In the beginning, while they were selecting for the cells, it was there. It was active. Otherwise, you know, well, they can also select for it with glufosinate, but very often it is a belt and braces approach. So you select for it with the antibiotic, because the antibiotic is a cell poison, just like glufosinate. If you do not have the gene that breaks down or inactivates the cell poison, then you will die, as a cell that is. Definitely, or very likely, although we do not have the details, the antibiotic resistance gene was active in the cells.

MR ALESBURY: But then becomes inactive later on.

MAE WAN HO: Yes.

I have here, going back to the vectors, natural vectors, viruses, plasmids and transposons.

A virus consists of genetic material, which is represented with the squiggly line here, and wrapped in a protein coat, which is this knobbly coat around the genetic material. It sheds it overcoat on entering a cell, where it can then either hijack the cell to make many more copies of itself -- that is why it is called a virus -- or it can jump directly into the cell's genome. Plasmids are pieces of free, usually circular, genetic material that can be indefinitely maintained in the cell separately from the cell's genome and replicate with the cell.

Transposons, represented with a straight line here, are jumping genes, they are units of genetic material which have the ability to jump in and out of genomes, with or without multiplying themselves in the process. Genes hitchhiking in these genetic parasites, therefore, have a greater probability of being successfully transferred into cells and genomes.

There are two ways, as you notice, for the gene to hitchhike a virus, which is not available to the plasmids or transposons. The usual way is for the genetic material, the foreign gene, to be integrated into the genetic material of the virus itself. The other way is for the foreign genetic material to be wrapped up in the protein coat, along with the genetic material of the virus. In the other cases, the foreign genetic material has to be spliced into the plasmids or the transposons before they can be carried around.

Natural genetic parasites are restricted by the same kind of species barriers that I have talked about earlier. So, for example, pig viruses will infect pigs but not human beings, and cabbage virus, such as the CaMV, will not attack tomatoes. It is the protein coat of the virus that determines host specificity. This is why naked viral genomes, that is, the genetic material stripped of the coat, have generally been found to have a wider host range than the intact virus.

Similarly, the signals for propagating different plasmids, such as the origin of replication, and transposons are usually specific to a limited range of host species, although there are exceptions to the rule.

Artificial vectors, however, are especially designed to overcome species barriers and to invade genomes. An artificial vector can transfer, say, GM constructs containing human genes spliced into it, to the genomes of all other mammals, or of plants. Artificial vectors greatly enhance horizontal gene transfer -- this means gene transfer across species barriers.

In making GMOs, the GM construct is generally spliced into an artificial vector and vector sequences often end up in the resultant GMOs, even parts of the vector that are not intended to do so. This gives rise to uncharacterised, unknown sequences that may not be safe.

Let me just show you this next transparency, where you have, say, a GM construct and this is a plasmid. Plasmids usually already have antibiotic resistant genes, but many of them, the artificial ones that are made commercially, have additional ones put in.

If you splice your GM construct, GM expression cassette, into the vector, you end up then with a construct that has the vector including the gene that you want for, say, herbicide resistance, or herbicide tolerance, plus an antibiotic resistant gene. Then this is made to infect cells. This is a diagram of a cell with three different chromosomes. Actually cells have many more different chromosomes.

There are two fates for the vector: one is to replicate in the cytoplasm in the cell, outside the genome; the other is to jump into the genome.

Chardon LL was made by splicing the *pat* gene expression cassette into the artificial vector pUC18, which already contains the *AmpR* gene. The pUC18 vector is derived from a naturally occurring plasmid, called ColE1, belonging to the gut bacterium *E. coli*, which is joined with part of a transposon, another genetic parasite, that contains the *AmpR* gene.

The pUC18 is maintained in high numbers of copies in the *E.coli* cell on account of a very active origin of replication. This is a signal for the DNA copying enzyme and machinery to latch on to the plasmid and to make many copies of it.

Therefore, it offers a convenient way to bulk up the GM construct, as the vector itself is being bulked up. Chardon LL, therefore, contains almost all of the pUC18 plasmid vector sequence as well as the *pat* gene expression cassette.

The genetic engineer cannot control where and in what form the GM construct becomes integrated into the genome. Each GM line is the result of one or more 'transformational' events in a single plant cell, shown here, in which the GM construct integrates into the cell's genome. An entire plant is grown from that cell, the progeny of which constitutes the GM line. In fact, several plants can be grown from the same cell by letting the cell multiply first, before inducing them to develop into plantlets in tissue culture.

Because transformation is random, each transformed cell, and hence the GM line derived from it, will be distinct, despite the fact that the same GM constructs and the same plant cells are used.

Often different plants derived from the same original transformed cell will also be different. This is something called 'somaclonal variation'. It happens very often in tissue culture. I shall come back to that later.

GM constructs are also structurally unstable, and are frequently re-arranged -- that means the order of the genes gets scrambled up -- deleted, some of the gene genetic material may just be thrown out, or repeated in part or in whole when they are integrated into the host genome. The resultant GMOs, likewise, are unstable and do not breed true, as significant genetic and epigenetic changes may occur in subsequent changes. Epigenetic is meant, in this context, changes which do not affect the sequence of these A, C, T, G alphabets that go along the DNA molecule. These changes then multiply the unpredictable risks to health and biodiversity.

MR ALESBURY: In relation to that concept, in particular the point that is at the end of the preceding paragraph where you say, "Because transformation is random, each transformed

cell, and hence the GM line derived from it, will be distinct", I can understand the concept actually, what you are getting at there, but when, as Aventis was doing, you are trying to produce a particular genetically transformed seed crop, does this point about each transformed cell being distinct apply to that? Or is there another stage? In other words, is it the case that all of the cells within Chardon LL have been transformed but in a whole variety of different ways? Or is it that something in the process that is then applied selects it down just to one, which will come out in a particular way, albeit that the transformation exercise is a bit hit or miss and random?

MAE WAN HO: You are ahead of me, as usual. I shall come to that very, very important point.

First, I just happen to have this slide made to document the structural instability of GM constructs, which is very well-known, so well-known that it is a topic in a standard textbook on genetic manipulation. It is Old and Primrose, 1994, *Principals of gene manipulation*, the fifth edition, Blackwell Science, Oxford.

MR ALESBURY: I can see that is one of your footnotes. Is it one of these documents as well?

MAE WAN HO: I will come to that, yes. I just want to show you other examples from the scientific literature. Here is a scientific paper, published in the journal *TIBTECH*, issue 17, pages 169 to 174. The authors are Prazeres *et al.* It is on "Large-scale production of pharmaceutical grade plasmid DNA for gene therapy problems and bottlenecks". As I mentioned before, GM constructs are the same whether it is for pharmaceutical purposes or agricultural purposes.

It says here in this paper:

"Structural stability, which leads to problems such as the formation of multimers is more difficult to" -- I think it should have been structural *in*stability:

> "Structural instability, which leads to problems such as the formation of multimers is more difficult to eliminate. These genetic stability problems of plasmids usually increase with the size of the DNA fragment inserted."

In another comprehensive review, published in 1996 by Pawlowsky and Somers in *Molecular Biotechnology*, volume 6, pages 17 to 31, "Transgene inheritance in plants genetically engineered by micro projectile bombardment"-- this is one of the methods of making transgenic plants, where you shoot the DNA, coated in particles of metal, gold or tungsten, into the cells and hope that they end up in the genomes.

MR ALESBURY: I have heard about that method, but I have not actually heard the reference to the gold and tungsten and so forth before. That is a novelty for me.

MAE WAN HO: It says here:

> "Molecular analysis of transgenes introduced by direct gene transfer often reveal that a high frequency of transgenic events exhibit extensive rearrangement of transgenic DNA sequences.

> Rearrangements of transgenic sequences are either deletions or ligations [that is joining] of introduced DNA."

In another place, it says:

> "Loss of transgene sequences during plant regeneration and reproduction has been described in a number of cases. All or only a portion of the transgene sequences may be eliminated."

There is yet another example, which I will not bore you with, but I would like to refer to the next item, BG1/C. This is a scientific paper by P Bregitzer, Halbert and Lemaux. It was published in *Theoretical and Applied Genetics*, volume 96, pages 521-425, 1998.

MR ALESBURY: It is called, "Somaclonal variation in the progeny of transgenic barley".

MAE WAN HO: In this paper, they compared the agronomic performance of transgenic plants with non-transgenic parent plants from which the transgenic lines were derived.

They also compared the agronomic performances of what they call transgenic derived null (non-transgenic) lines. What are these? These are plants that were made transgenic, but, in the course of regenerating the plant, or in the course of growing them in the field, or in the greenhouse in subsequent generations, they have lost either the expression or, in this case, which I suspect, they have lost the foreign genes, the GM constructs, completely. Although because they have not provided molecular genetic data, we are not sure.

MR ALESBURY: So they are still different from what they started with, but they have lost the peculiar inserts.

MAE WAN HO: They have probably lost the insert. What is very striking, if I may refer you to table 1 on page 423. Here, it says:

> "Table 1, percentage of individual transgenic plants grown at two locations in 1994, showing the most common morphological variations ."

Down the first column are listed family. In the footnote, it explains:

"Each family represents an individual transformation event", which means that it came from one transformed cell.

But, as I said before, you can let the cell multiply, and then you end up with a whole family which should have the same transformational event and should be the same. However, as you can see from the table, there is a wide range of variations with respect to the three most common agronomic properties, extreme dwarfism, semi-prostrate habit, extremely late maturity.

MR ALESBURY: These are the three most common bad things.

MAE WAN HO: You can see that the percentages vary quite widely within each family. Of course between families they are very variable. This really alerts you to the kind of unpredictability, uncontrollable nature and the variable nature of these transformational

events and, therefore, the GM lines derived from them.

Table 2, shows agronomic performances of transgenic barley grown at two locations in 1994, expressed as percentage of the non-transgenic control. Again, you can see that for practically all of them they have reduced height, reduced yield. The reduced yield can be up to over 80 per cent, because the yield can be as little as16 per cent of the non-transgenic. Also, the seed weight is reduced.

I then refer you to the next page, Table 4, agronomic performances of Golden Promise, that is the original parental non-transgenic line, and transgenic derived null segregant barley lines grown in 1996.

As I explained before, these were transgenic lines to begin with, but they have lost the transgenic insert or the transgenic characteristics. Here, you can see also that for all the agronomic performances they were much worse than the parental line.

What it means is that, even though this kind of instability may lead to loss of function or loss of the genes themselves, they leave a footprint -- the GM constructs leave a footprint in the genome of the GMOs, which is then expressed as this kind of worsened agronomic performance.

MR ALESBURY: I think I have two things. One, I think that substantially answers that question I asked earlier, about how you do get these peculiar variations even within what is supposed to be the same transformed version of the plant concerned. I think this information deals with that point.

I suppose I ought to ask, slightly from the other direction, does the fact that these examples which are to do with barley all show the transgenic plants or these null segregant versions -- the concept of which I understand -- to be worse -- I accept that, that that is what is shown here. It might be said -- and since no one else is asking questions I had better ask this question -- that that is what this paper shows about these types of barley which we are looking at. Might it not be the case that other transgenic plants, whether barley or maize, to take an obvious example, contrary to this, might show better performance?

MAE WAN HO: That is a very good question. I actually have further papers in my bag which I will not take out.

MR ALESBURY: You can see it is a question which follows from being shown this sort of information. These look bad. The argument might be that other transgenically treated barley might have better performance.

MAE WAN HO: There are -- let me say -- a substantial number of papers on other species such as rice, oats, wheat and so on, showing the same kinds of instability. However, so far as I am aware, no one has looked at the footprint question that you are raising, which is very important. You see, this brings up the most worrying aspect of the current scene, because genetic engineers and scientists are so heavily absorbed into the commercial sector, they are far too busy exploiting the technology, and they are not doing sufficient experiments, good quality experiments of the kind that I have just quoted. Many more of these experiments

ought to be done.

In fact, if you return to this paper, BG/1C, it says in the conclusion on page 422, the first complete paragraph:

> "The impact that SCV (which is short for somaclonal variation) will have on the application of genetic engineering technology to barley cultivar development has not yet been documented, but the evidence suggests that SCV may be of considerable importance."

Again, on the first page at the end of the extract, it says:

> "Attempts to understand the sources of SCV and to modify transformation procedures to reduce the generation of SCV should be made."

You can see that the state of research is, to say the least, not very advanced, but already people are finding these problems.

The gist of it is that, unless there are good molecular genetic data documenting the genetic stability of the GM line, it is impossible to guarantee that it is stable or uniform to begin with, or that it will not change further in subsequent generations, especially with regard to properties that affect safety.

Unfortunately, regulators in Europe, Canada and the United States all appear to be unaware of this. They have not required industry to submit molecular genetic data in sufficient detail to document genetic stability, or to allow identification of the GM line unambiguously. Instead, they are effectively granting blanket approval for GMOs from multiple transformation events, plus all progeny arising from them variously back-crossed to non-GM varieties.

Here, I would like to refer to the next item, supporting documents that I have brought along; BC/1D. It was a submission that I have made myself to the Biotechnology Group of the Trans-Atlantic Economic Partnership on the Molecular Characterisation required for GMOs. On the next page, the opening paragraph, it explains where this came from, where the molecular characterisation requirement came from.

A pilot project was set up by the Biotechnology Group in the Trans-Atlantic Economic Partnership Action Plan, TEP for short, to compare the molecular genetic characterisation that industry has to submit on both sides of the Atlantic to gain regulatory approval for release to the environment.

The processing of a simultaneous application to both sides of the Atlantic from industry will then be monitored. This TEP is generally regarded as a Trans-Atlantic Free-Trade Agreement. This pilot project is the first step towards harmonisation of GMO regulation and trade.

A joint EU/US workshop was held in Luxembourg on 19th-21st October 1999. The key outcome of the workshop would be a technical annex, annex 3, of the molecular genetic characterisation required on both sides of the Atlantic. A draft annex 3 circulated for comments after the workshop was actually drawn up as a result of an earlier meeting of

regulatory officials from the United States and Canada, aimed at comparing and harmonising the molecular characterisation of the two countries. My comments are addressed to this draft annex 3.

I will not go into details, except to point out that I said to them, that it is very important to distinguish between functional instability, the fact that the gene is no longer expressed and structural instability, the fact that the gene is scrambled up, the GM constructs are scrambled up, or they have been lost altogether.

So functional stability and structural stability have both to be documented. It is necessary, therefore, to provide data on evidence of stability, molecular genetic data of genetic stability, in successive generations.

On page 4 of this document I propose adding a whole new paragraph, or Section number "2, molecular identity of the transformed line. 2.1, the transformed line must be identified in terms of its transgenic DNA as follows" -- for transgenic DNA, read GM construct:

"(a) total number of inserts of transgenic DNA", because very often you can have more than one insert in the same cell;

"(b) location of each insert, whether it is an organelle or in the chromosome." Organelle, such as the mitochondria, or the chloroplast. Mitochondria are the powerhouses of the cell, and the chloroplasts are the ones that contain the green pigment that allows green plants to absorb sunlight in order to transform energy and material. They also have genetic material;

"(c) precise position of each insert, where on which chromosome."

"(d) structure of each insert, whether it is duplicated, deleted, re-arranged, et cetera"

"(e) complete genetic map of each insert, identifying coding regions, marker genes, non-coding regions, promoters, introns" -- these are all different kinds of genetic material -- "leader sequences, terminators, enhancers, origins of replication, origin of transfer"(another important signal that allows the genetic material in plasmids to be transferred from one bacterium to another). "T-DNA borders"(these are some parts of plasmids that are used in genetic engineering), "plasmid sequences, linkers, *et cetera* , including any truncated incomplete sequences."

"(f) the complete base sequence of each insert."

"(g) the base sequence of at least ten kilo base pairs of flanking host genome DNA on either side, including changes in methylation patterns." This is very important because, in order to identify where the insert is, you want to know the genome sequence on either side that will more or less pinpoint where in the chromosome it is, where in the genome it is. Methylation patterns are just chemical modifications of the DNA, which is usually associated with gene silencing, which means that the gene is not active any more. The way this is important is because the insert itself can affect the activity of genes quite far away from it.

"(h) appropriate molecular probes for each insert, with flanking host genome or organelle

sequences, which can be used to monitor the structural stability of the insert." You have to have probes, basically, which includes the flanking genetic material of the host, otherwise you cannot tell whether it has stayed in the same place.

Item "2.2. Each transformed line must be identified in terms of total protein profiles to monitor for unintended changes in the pattern of gene expression.

"2.3. Each transformed line must be identified in terms of metabolic profiles to monitor for unintended changes in metabolism."

You see, I have drawn attention to the morphological changes earlier, but more important from the safety point of view are, whether there are other genes expressed which should not be expressed, and other metabolites or chemicals that have increased in concentration, which may not be safe, and so on.

Going back to the main text, Chardon LL does not satisfy this kind of stability requirement which is already incorporated in something called the DUS test. The product approved under the entity Chardon LL (Aventis T25) is stated as "Seeds of maize line HE/80 transformation event 25 and any progeny derived from crosses of event T25 with traditional corn varieties". But no molecular genetic data documenting the stability or homogeneity of the seed have been provided.

European Commission legislation actually requires that new plant varieties be tested for distinctness, uniformity and stability (or DUS for short) prior to being placed on the National List of a Member State and prior to marketing. There is no evidence that any GM line, let alone Chardon LL, has passed this test, which requires the molecular genetic data that I have mentioned. Incidentally, this also invalidates patents on transgenic lines and organisms.

The GM insert in Chardon LL has almost the entire pUC18 sequences -- the plasmids sequence -- plus the *pat* gene cassette, but the *AmpR* gene has been disrupted in its promoter region, which is why it is not active. This is a sign of structural instability. Most worrying, the GM insert includes the origin of replication for the pUC18 plasmid used as a vector, which introduces its own risks.

I will now summarise the special safety concerns arising from GMOs in a more systematic way. There are four special safety concerns arising from GMOs, which were first outlined for the Minister of State for the Environment, Michael Meacher, in a paper entitled, "Special safety concerns of transgenic agriculture and related issues; briefing paper for the Minister of State for the Environment, the Right Honourable Michael Meacher".

It was written after he invited myself to debate with molecular geneticists in his office. This paper was subsequently published in the proceedings on a conference on biosafety law, organised by the Centre of Judiciary Studies of the Federal Council of Justice in Brazil.

MR ALESBURY: What are you actually reading from now?

MAE WAN HO: It is on page 10, the reference.

MR ALESBURY: I only have up to page 9 in mine. Are there a lot of references after page 9?

MAE WAN HO: There are up to 28.

MR ALESBURY: I have not actually ended up with that last page.

MAE WAN HO: Maybe I have another copy. (Handed)

There are four special safety concerns. The first, effects due to the exotic gene product (or products) introduced into the transgenic organisms or the GMOs.

The second, unintended, unexpected effects due to the random insertion of the GM constructs; and interaction between the genes in the GM constructs and the host genes.

The third special safety concern of GMOs is effects associated with the nature of the GM constructs.

The fourth are effects of gene flow, especially horizontal spread of genes and gene constructs from the GMOs to unrelated species.

You have mentioned something about lunch, and I did not know whether you want me to go on or whether you wanted to stop?

MR ALESBURY: We have our lunch break at about one o'clock, which we are still quite some way off.

MAE WAN HO: Let me explain these safety concerns.

Hazards from exotic gene product (or products) introduced. The exotic genes, as we have seen, are mainly from bacteria and non-food species. Furthermore, the expression of these genes is often greatly amplified by strong viral promoters,. In practice, that means all species interacting with the GM plants -- from decomposers and earthworms in the soil to insects, small mammals, birds and human beings -- will be exposed to large quantities of proteins new to their physiology.

Adverse reactions may occur in all species, including immune or allergic responses. For example, Bt toxins from the soil bacterium *Bacillus thuringiensis*, engineered into GM crops to kill insects pests, are found to harm beneficial insects such as lacewings and endangered species such as monarch butterflies and the black swallowtail.

At this point I would like to refer to BC/1A. I draw your attention to page 5, paragraph 9. The threats to biodiversity from major GM crops already commercialised are becoming increasingly clear. The broad spectrum herbicides used with herbicide tolerant GM crops decimate wild plant species indiscriminately. They are also toxic to animals. Glufosinate causes birth defects in animals -- that being the herbicide used with Chardon LL. Glyphosate is linked to non-Hodgkin lymphoma. GM crops with Bt toxins kill beneficial insects such as bees and lacewings, and pollen from Bt corn is found to be lethal to monarch butterflies as

well as the swallowtails.

Now I would like to draw your attention especially to the footnote, number 33, which is the scientific paper describing the swallowtail experiment. The title says, "Absence of toxicity of *Bacillus thuringiensis* pollen to black swallowtails under field conditions". This is published, by the way, in a high prestige journal, PNAS, in the United States. But if you read the paper carefully, despite the claim in the title, the paper reports toxicity of Bt pollen from a high expressing line to swallowtail larvae in the laboratory. In fact, it killed 80 per cent or more of the larvae.

We have reviewed this paper in detail in *ISIS News* number 5, which is to be found on our website, which goes to show that you cannot accept scientific papers on face value. You have to understand the science and you have to read it carefully.

The Bt toxins come in many kinds. One of them, the Cry9C in Aventis's Starlink GM maize, intended for animal feed, is a potential allergen for human beings and is behind the recent massive recall of contaminated taco shells in the United States.

MR ALESBURY: That is a different GM maize from Chardon.

MAE WAN HO: Yes.

Actually other Bt toxins may also be allergenic. It is reported -- and let me see if I should refer to this. Maybe in the interest of saving time, I shall just refer to this paper which was produced for us in BG1/E by Professor Joe Cummins of the University of Western Ontario. This is a very useful summary of *Bacillus thuringiensis* and its toxins as biopesticides, showing, as I said, that other Bt toxins may also be allergenic.

We turn to Chardon LL. How safe is the *pat* gene product? That is the only gene product they claim is expressed by the GM construct. It originates, as you have said, in Cameroon, from the soil bacterium *Streptomyces viridochromogenes*, which has never been part of our food chain, nor animal feed. The *Streptomyces* genus includes plant as well as human and animal pathogens. Aventis conducted a feeding trial for 14 days on the extracted protein, and that was not obtained from Chardon LL but from GM oilseed rape. The rats are monogastrics (with one stomach) and have a completely different digestive system from ruminants, which have four stomachs and keep the plant material much longer.

Furthermore, the feeding experiment was never completed and no histological data on the state of internal organs was ever presented. As has been argued by Dr Pusztai and others, feeding studies must be done on young animals, as the young are more susceptible to adverse effects, and histological examination is crucial.

I understand that Dr Pusztai has independently criticised the feeding studies.

Hazards from random gene integration and interaction with host genes. The random, uncontrollable insertion of GM constructs into the host genome and the interaction of exotic genes with host genes is well-known to give many developmental failures and gross abnormalities in animals, as well as in plants, as we saw in the scientific paper that I referred

to earlier.

In micro-organisms and plants, unexpected toxins and allergens have been found. The most notorious case involved a genetically engineered batch of tryptophan that killed 37 and made 1,500 seriously ill, as mentioned in our World Scientists Open Letter, which is BG/1A, paragraph 10, page 6.

Products resulting from genetically modified organisms can also be hazardous, for example, a batch of tryptophan produced by GM organisms was associated with at least 37 deaths and 1500 serious illnesses.

MR ALESBURY: What is tryptophan, just briefly?

MAE WAN HO: This is very crucial because at the moment we can only test for transgenic crops and products if they contain the gene product that is put in, or the DNA, the GM construct. However, there are lots of products, including tryptophan (which is an amino acid), sold in health food stores which contain neither protein nor DNA, or *should* contain neither protein nor DNA. So they will be slipping through the regulatory net.

There were no attempts to characterise Chardon LL for unintended toxins and allergens, because industry is not required to do so. Now, in the case of tryptophan, they knew it was a genetically engineered batch of tryptophan. It was produced by a Japanese biotech company. But by the time they investigated it, it was six months later, the company had the chance to remove any evidence that might have been useful. All they could tell was that it was not the tryptophan itself, it may be some contaminants. The difficulty was that we do not know if it was associated with the genetic engineering, because they also changed the method of purification. So, you see, sometimes the trouble can come from contaminants that are very, very minor.

Ewen and Pusztai carried out feeding studies with GM potatoes, from which they concluded that significant effects may be due not only to the protein product, gene product that they put in, but due to the transformation process, or the GM construct.

Again, I remind you of the paper that I referred to in BG/1C; how merely going through the transformation process can leave footprints in the genome, even though the GM plants were not expressing the gene or they may not even have the transgene any more.

The transgenic process itself, that paper also revealed, introduces extra variation, apart from those due to the tissue culture process. I draw attention to this to emphasize that there is a kind of consistency in the available scientific evidence, which I think should be taken seriously.

As yet, our Government have made no attempts to try to get those investigations [of Ewen and Pusztai] repeated. In the case of Chardon LL, they seem to be avoiding the issue altogether by accepting feeding data on the novel protein alone, in granting approval.

Hazards from the GM construct. Safety concerns have been indeed raised over the 35S promoter from the Cauliflower Mosaic Virus. I understand that my co-author, Angela Ryan,

has already dealt with this in great detail.

MR ALESBURY: She was here the other day, yes.

MAE WAN HO: This construct, this Cauliflower mosaic viral promotor, is in the GM construct of practical all GM crops already commercialised or undergoing field trials. We have published a series of scientific papers. I have included them here in BG/1F to BE/1H. Two of the early ones have been submitted by Angela Ryan.

MR ALESBURY: BG/1 F and BG/1G, I think is the reply to the critique. She certainly produced those two.

MAE WAN HO: The new one that is included here is one that is in press, BG/1H. I just do a brief summary on what we have shown in these three papers.

CaMV is closely related to human hepatitis B virus and less closely to retroviruses such as the AIDS virus. Why is this important? Because related viruses can more readily exchange genes than non-related ones. They also use similar regulatory signals such as promoters. Although they have never tested whether CaMV promoter can substitute for the hepatitis B virus, or for the AIDS virus, scientists have shown that this [CaMV] promoter can indeed substitute in part or in whole for promoters of other viruses to give infectious viruses.

Although the intact CaMV virus itself specifically infects the plants of the cabbage family, its isolated 35S promoter, cut out of the virus, and then put in the GM construct, is found to be promiscuous across domains and kingdoms of living organisms. It is active in all plants, algae, yeast and bacteria, and, as we recently discovered in the scientific literature, ten years old, also in animal and human systems.

The conventional wisdom among plant molecular geneticists is that CaMV 35S promoter is only active in plant and plant-like species. Why have they not checked the literature before using it so widely?

Let me just refer briefly to BG/1H. I want to draw your attention to the second last paragraph before the references. It reads, "The conventional wisdom among plant molecular geneticists is that plant promoters such as the CaMV 35S are not active in animals. In fact, the CaMV 35S promoter was found to support high levels of reporter gene expression in mature Xenopus oocytes . . .

(aside: reporter gene is merely a gene which you can link to a promoter, or something that you want to find out, "Does it work or not?" Then you look at this gene to see if it is active. So it reports on whether this thing you put in acts as a promoter. Xenopus is actually the African clawed toad, which is a frog. Oocyte is the unfertilised egg.)

" . . . and to give very efficient transcription in extracts of Hela cell nuclei. (Aside: Hela cells are a human cell line.) The CaMV promoter worked at least as well as the SV40 promoter in Xenopus oocyte. (Aside: SV40, by the way, is a virus that originated from monkeys, but is now increasingly found to be associated with all kinds of human cancers. It is suspected that contaminated vaccines containing the SV40 virus have gone into the human population and

has led to cancer.)

" . . . . The CaMV promoter worked better than the major late promoter of the adenovirus 2 in Hela cell extracts. Adenovirus is a cold virus which is very often used in gene therapy. By the way, that is a very risky business, where you are making transgenic human beings. They have already discovered at least six deaths and 650 adverse events, which went unreported by the biotech companies on grounds that these were 'commercially sensitive information'.

I draw your attention to that just to emphasize that we are playing with fire when we play with these GM constructs that are, as I say, similar across animals, plants and human beings.

These findings suggest that the CaMV 35S promoter has the potential to reactivate dormant viruses, which have now been found in all genomes, plants and animals included.

MR ALESBURY: You did not actually deal with that bullet point about the recombination hotspot.

MAE WAN HO: Sorry.

The CaMV 35S promoter has a 'recombination hotspot' -- and I gather that Angela gave you a very detailed account of the recombination hotspot -- where it is prone to break and join up with other genetic material, hence increasing the likelihood for horizontal gene transfer and recombination.

I shall go into more details about horizontal gene transfer later. Again, looking back at this paper, BG/1H, it says:

"CaMV 35S promoter fragmentation hotspot confirmed."

This refers to a very good paper by other scientists who confirm the findings of Kohli et al, quoted in reference 4 in this paper, which Angela has gone over in detail with you. Kumpatla and Hall's paper confirm the findings of Kohli et al. It is a very good paper by the way.

These findings suggest that CaMV 35S promoter has the potential to reactivate dormant viruses, which have now been found in all genomes, plants and animals included, and to recombine with other viruses, dormant or otherwise, to create new viruses.

I draw your attention to Ewen and Pusztai's findings in their paper published in the *Lancet*, where they said that the GM construct or the transformation process itself may have significant effects. They also reported increases in white blood cell counts in the gut tissues. He [Pusztai] told me personally that was a sign, a non-specific sign of viral infection. Now, unfortunately his grant was cut off and they could not carry out the crucial experiment to test their hypothesis [that viral infection did take place].

In addition, the fact that the promoter is active in animals and human cells means that, when transferred into their genomes, it may result in overexpression of genes that are associated with cancer.

Therefore, as we put it, there is a strong case for recalling all GM crops containing the CaMV 35S promoter from environmental release on grounds of safety.

I would also like to mention something else in relation to the reactivation of dormant viruses in cells, which comes in -- I am sorry, I am going to take something out of order. We can refer to BG/1J. It is a paper that is an update on an earlier report we have produced on "Unregulated hazards, 'naked' and 'free' nucleic acids, which I gather my colleague Angela Ryan has submitted to this hearing.

MR ALESBURY: She did, yes.

MAE WAN HO: This is an updated version. I would like to draw your attention to page 9 of this document ["Slipping through the regulatory net, 'naked' and 'free' nucleic acids"], the second full paragraph:

> "As all viral promoters have one or more modules in common, it is not inconceivable that the CaMV 35S promoter may recombine in part or in whole with dormant or relic viral sequences in the genome to regenerate infectious viruses. Synthetic super-promoters for gene therapy have already been created in the laboratory by random recombination of modules isolated from natural promoters."

This really shows it can happen. The next paragraph is important:

> "In gene therapy, a major safety concern is indeed the generation of replication competent viruses (RCV for short) due to recombination of viral vectors with proviral and other sequences in the genomes of cell lines used to package the viral vectors."

This, again, shows you that it is possible to wake up dormant viruses by recombination.

Chardon LL does have a 35S promoter and is, hence, subject to all the potential hazards that it brings.

In addition, it has an 'origin of replication' for the PUC plasmid vector, plus further stretches of uncharacterised, unidentified sequences of unknown function and safety belonging to the plasmid, as we have mentioned in ISIS's written objection.

The 'origin of replication', claimed not to be active in plant cells, will be active in bacteria to which the GM construct is transferred. There is a possibility that it can be transferred. This signal, as I have said before, enables the GM construct linked to it to be maintained in the bacteria as an independently replicating plasmid of high copy numbers, hence enabling the GM construct to be multiplied and spread widely by horizontal gene transfer.

Finally, the hazards from gene flow, especially horizontal gene transfer. GM constructs can spread by ordinary cross-pollination to non-GM species of the same species or related species. The most obvious effects of cross-pollination already identified are in creating herbicide tolerant weeds and superweeds. I draw your attention, again, to paragraph 8 of BG/1A on page 5.

> "Some of the hazards of GM crops are openly acknowledged by the UK and US Governments. The UK Ministry of Agriculture Fisheries & Food (MAFF) has admitted that the transfer of GM

> crops and pollen beyond the planted field is unavoidable. This has already resulted in herbicide tolerant weeds. An interim report on UK Governments sponsored field trials confirmed hybridisation between adjacent plots of different herbicide tolerant GM oilseed rape varieties which gave rise to hybrids tolerant to multiple herbicides. In addition, GM oilseed rape and their hybrids were found as volunteers in subsequent wheat and barley crops which had to be controlled by standard herbicides. Bt resistant insect pests have evolved in response to the continuous presence of the toxins in GM plants throughout the growing season and the US Environmental Protection Agency is recommending farmers to plant up to 40 per cent non-GM crops in order to create refugia for non-resistant insect pests."

Another consequence is the spread of novel genes and GM constructs for over expression, as well as the antibiotic resistance marker genes. This will multiply the unpredictable physiological impacts on organisms to which the genes and gene constructs are transferred, and hence on the ecosystem.This whole area has yet to be investigated.

By far, the most serious consequences are from the horizontal transfer of GM constructs to unrelated species, in principle, to all species interacting with the released GMO: micro-organisms, earthworms and arthropods in the soil, insects, birds, mammals, human beings.

I have reviewed horizontal gene transfer in detail in two commentaries, which I hope are here. Actually, the commentaries are not here because of copyright reasons, but they will appear on the website of SCOPE, which is a United States National Science Foundation funded research project involving the *Science* Journal and groups in the University of California and the University of Washington in Seattle, the purpose of which is to provide adequate information and a forum for discussion and debate.

I was invited to write two commentaries on horizontal gene transfer. The paper that is provided here is one that I have independently put out on the ISIS website, which is almost the same as the two commentaries.

MR ALESBURY: Is that BG/1I.

MAE WAN HO: That is right.

Horizontal gene transfer is not just a theoretical possibility. There is already evidence that GM genes from GM plant material can transfer to soil bacteria and fungi. Some scientists actually did the relevant experiments. If we go to page 10 [of BG/1I], I think, it says the following,

"Secondary horizontal transfer of transgenes and antibiotic resistant marker genes from genetically engineered crop plants into soil bacteria and fungi have been documented in the laboratory. Transfer to fungi was achieved simply by co-cultivation. (I refer you to the reference cited in footnote 37.)

"While transfer to bacteria has been achieved by both, re-isolated transgenic DNA and total transgenic plant DNA. (This, again, is documented in the scientific literature cited in footnote 38.)

"Successful transfers of a kanamycin resistant marker gene to the soil bacterium were

obtained using total DNA extracted from homogenised plant leaf from a range of GM plants" -- I will not read the Latin names -- "potato, tobacco, sugar beet, oilseed rape, tomato. It is estimated that about 2,500 copies of the kanamycin resistant gene, from the same number of plant cells, (assuming that they only had one insert per plant cell and one copy per plant cell, and very often that is not clear, because the molecular genetic data provided is not adequate, they show that the number of copies) is sufficient to successfully transform one bacterium, despite the fact that there is a one million fold excess of plant DNA present. A single plant with say, 2.5 trillion cells, would be sufficient to transform one billion bacteria.

Despite the misleading title of one of the publications -- in fact the actual publication itself is listed under the footnote 38, it is Schluter et al, the title says, "Horizontal gene transfer from a transgenic potato line to a bacterial pathogen, *Erwinia chrysanthum*, occurs, if at all, at an extremely low frequency".

Unfortunately, when you actually read the paper itself, it tells us a somewhat different story. In fact, in the laboratory, they found a very high gene transfer frequency of 5.8 per 100 recipient bacterium, 10 to minus 2 means per 100. But the authors then proceeded to calculate an extremely low gene transfer frequency of 2.0 times 10 to the minus 17, an impossibly small number, under extrapolated natural conditions, but they do not know what the natural conditions are, and they also assume that different factors acted independently.

The third paragraph in BG/1I]:

> "Defenders of the biotech industry still insist that just because horizontal gene transfer occurs in the laboratory does not mean it can occur in nature."

Why the hell bother doing laboratory experiments? Please excuse my language.

> "However, there is already evidence suggesting it can occur in nature. First of all, genetic material released from dead and live cells is now found to persist in all environments and not be rapidly broken down as previously supposed. It sticks to clay, sand, humic acid particles, and retains the ability to infect or transform a range of micro-organisms in the soil. The transformation of bacteria in the soil by DNA absorbs to clay, sand and humic acid has been confirmed in microcosm experiments."

Importantly, the next paragraph:

> "Researchers in Germany began a series of experiments in 1993 to monitor field releases of transgenic sugar beet, containing the marker gene for kanamycin resistance, for persistence of transgenic DNA and of horizontal gene transfer of transgenic DNA into soil bacteria . It is the first such field experiment to be carried out; after tens of thousands of field releases and tens of millions of hectares have been planted with transgenic crops. It will be useful to review their findings in detail.
>
> "Transgenic DNA was found to persist in the soil for up to two years after the transgenic crop was planted. Though they did not comment on it, the data showed that the proportion of kanamycin resistant bacteria in the soil increased significantly between 1.5 and two years. Could it be due to horizontal gene transfer of antibiotic resistance marker gene in the transgenic DNA?" That is an open question. "Although none of the 4,000 colonies of soil bacteria isolated, a rather small number, was found to have taken up the transgenic DNA by the probes available, two out of the seven samples of total bacterial DNA they have prepared yielded positive results after 18 months."

The time delay is because, probably, it takes time for the plant residue to decay and release the DNA. It might also indicate that there could be further amplifications of the GM DNA, due to the GM DNA having been transferred into bacteria that divide and grow, so that the DNA will be amplified along with growth of the bacteria.

> "This suggests that horizontal gene transfer may have taken place, but the specific strain which has taken up the transgenic DNA cannot be isolated as colonies. That is not surprising, as less than one per cent of all the bacteria in the soil is culturable" (can be cultured).
>
> "The authors were careful not to rule out transgenic DNA being absorbed into the surface of the bacteria rather than being transferred into the bacteria."
>
> "The researches also carried out microcosm experiments, to which total transgenic sugar beet DNA was added to non-sterile soil with its natural complement of micro-organisms. The intensity of the signal for transgenic DNA decreased during the first days, indicating breakdown perhaps, and then mysteriously increased again. This may be interpreted as a sign that the transgenic DNA has been taken up by the bacteria and become amplified as a result with the growth of the bacteria."

"In parallel, soil samples were plated", put on agar plates, "and the total bacteria was allowed to grow up for four days." So you isolate all the bacteria. You do not care which strains they are. After which, the DNA was extracted. "Several positive signals were found which [quoting the authors] "might indicate uptake of transgenic DNA by competent bacteria",

> "The authors were cautious not to claim conclusive results simply because the specific bacteria carrying the transgenic DNA sequences were not isolated. The results do show, however, that horizontal gene transfer may have taken place both in the field and in the microcosm experiments."

MR ALESBURY: You asked me to mention to you about what is the normal time we stop for lunch. I do not want to stop you in the middle of paragraph or anything, but we have reached that point. You go on to a point that is convenient to stop. I do not think we will finish before lunch.

MAE WAN HO: I will finish this paragraph. Just to say that there is already evidence that GM genes -- you see you have to look at GM constructs across biomedical uses and agricultural uses. So I am drawing, again, on recent experiments in so-called gene therapy.

They have amply documented [in gene therapy experiments] that GM constructs, of the same form as those used in GM crops, can readily invade cells and genomes of animals and human beings. One of the routes of gene therapy is oral administration, that is, swallowing. I shall come back to this.

MR ALESBURY: Is that--

MAE WAN HO: I think maybe this would be a good time. You will give me guidance as to when you think I ought to continue, because I gather that there are other groups presenting evidence in the afternoon.

MR ALESBURY: There are, but we will proceed with you -- we normally have an hour, can everybody cope if we come back at 2.00, slightly less than an hour. I think, as a safety

precaution, we had better do that and we will carry on.

(Luncheon Adjournment)

MAE WAN HO: I was, before lunch--

MR ALESBURY: We were on page 7.

MAE WAN HO: --on the top of page 7. I was referring to some experiments in gene therapy. This is dealt with in BG/1J.

MR ALESBURY: That is the naked and free nucleic acids.

MAE WAN HO: Yes.

I would like to draw attention especially to page 5. The section begins:

> "The potential hazard of naked nucleic acids. Naked viral genomes often have a wider host range than the intact virus. Human T cells leukaemia viral genomes formed complete viruses, and naked genomes from the human polyoma virus BK or BKV gave a full blown infection when injected into rabbits, despite the fact that neither intact virus is infectious for rabbits."

I then want to continue on to the next paragraph:

> "Gene therapy vectors and naked DNA vaccines have caused acute toxic shock reactions and severe immune reactions."

I would like here to interject that all of these are backed up by references to the scientific and medical literature:

> "Between 1998 and 1999, scientists in the US drug companies failed to notify the regulatory authorities of 6 deaths and more than 650 adverse events resulting from clinical trials of gene therapy, the causes of which are yet to be determined.
>
> "Naked DNA can also trigger auto-immune reactions. Any fragment of double-stranded DNA or RNA down to 25 base pairs introduced into cells can induce those reactions which are linked to rheumatoid arthritis, insulin-dependent diabetes and Grave's disease of the thyroid.
>
> "Double-stranded RNA mainly appears during viral infections and is recognised as a trigger for activating genes that produce interferons."

These [interferons] are proteins that act against viruses. It is a means for the body to protect itself against viral infections.

> "Many spontaneous mutations result from insertion of transposons" (these are one class of genetic parasites) "and other invasive elements. Insertion mutagenesis is associated with a range of cancers of the lung, breast, colon and liver.
>
> "Finally, unintended modification of germ cells can result from gene therapy and vaccinations."

You have to understand that at the moment they say, "We are not doing germ line gene therapy; we are only doing somatic gene therapy", which means that you only modify the

cells of your body without modifying germ cells. But what they have been finding is that unintended modification of germ cells nevertheless occurs.

What else should I quote from here? I think maybe, for the time being, I want to find the passages that were connected with . . . on page 5, the third and fourth paragraphs:

> "Recent research in gene therapy shows how readily naked nucleic acids can enter practically every type of human cells and cells of model mammals. Naked nucleic acid can be successfully delivered, either alone or in complex with liposomes and other carriers" -- liposomes are just some lipids that form themselves into little bags, and you can trap your genetic material into these little lipid bags -- "in aerosols via the respiratory tract," breathing in, "by topical application to the eye," in eye drops, "to the inner ear, to hair follicles, by rubbing on the skin, by direct injection into muscle through the skin and by mouth" -- I think that is where I said swallowing -- "where the nucleic acid is taken up by cells lining the gut."
>
> "Naked DNA can even be taken up by sperms of marine organisms and mammals and transgenic animals created in that way. Researchers have also found unintended integration as, for example, of a plasmid-based naked DNA malaria vaccine injected into mouse muscle."

It was not supposed to integrate into the genome. It was not designed to integrate, but nevertheless it got integrated into the genome.

What is the probability of horizontal gene transfer in the gut, if animals eat Chardon LL and the GM material ends up in the gut? What is the probability that there is transfer to unrelated species? An important factor is whether the GM genetic material is sufficiently broken down in processed food and animal feed. The UK Government's own commission research has repeatedly shown that most commercial processing either left the genetic material intact or in large fragments -- large fragments are significant because they contain whole genes, perhaps with all their promoters and terminators intact, so they are readily functional. The scientists advised against using genetic GM material in animal feed -- this is in a report commissioned by MAFF. I have included our report of this report in the next [supporting document], BG/1K.

This report from ISIS is [entitled] "Transgenic DNA in animal feed". I draw your attention to page 3, the conclusions. You see, we went through this report with a fine toothcomb and translated it in such a form that it could be understood by ordinary people.

Conclusions:

"The results show that the DNA remains intact in fresh plant leaves and grain, as well as in silage, under even small-scale laboratory conditions" (where you would have thought things would work much better). "Temperatures of not less than any 95 degrees Centigrade for not less than 5 minutes were required to degrade DNA" to less than 25 base pairs. "Most commercially processed animal feeds are subjected to temperatures not exceeding 85 degrees. Where steam is used to condition material for pelleting, temperatures reached at least the mid-80s for an uncertain length of time. The laboratory results show that DNA may only be partially degraded under those conditions."

"The report" (the Government report, that is) "recommends against using ensilaged GM material for animal feed, and concludes that most commercially produced animal feed

contains intact DNA fragments of a size greater than 1200 base pairs, comparable to the b-lactamase antibiotic resistance marker gene used in many GM crops", including Chardon LL .

In fact, the UK Government scientists themselves have pointed out that that the possibility of horizontal gene transfer starts in the mouth, which contains dangerous bacteria that can take up antibiotic resistant genes. This is contained in a peer-review scientific paper, to which I shall refer presently.

Similar bacteria are present in the respiratory tract. They warn of dangers to farm workers and food processors from GM pollen and GM dust in a letter, which I have included here as BG/1L. It is a letter written -- the letter heading is from MAFF, the joint food safety and standards group. It is dated 4th December 1998. It was addressed to the Food & Drug Administration in the United States. It was giving advice to a document, which was sent by the Food & Drug Administration for comment on their guidance for industry, regarding use of antibiotic resistance marker genes in transgenic plants.

I refer you to page 2. On the top of page 2, it says:

> "It should be remembered that, while the production methods both for food and animal feed may denature the gene product" (which is the protein), "people may be exposed to it before this stage. For example, when a plant is grown or when people are actually engaged in the production process."

Of course, such dangers would apply to the general public as well because, if we have enough GM plants grown in the country, GM pollen, GM dust, would be everywhere.

Several months ago, there was a Professor Heinz Henrich Kaatz from the University of Jena in Germany, who reported that GM genes have transferred via GM pollen to bacteria and yeast living in the gut of the bee larvae. This also raises the issue of the safety of GM honey.

To return to Chardon LL, Chardon LL's ampicillin resistance gene is reported to be non-functional because its promoter is lost. However, this gene is notorious for its ability to mutate and extend the ability of the enzyme encoded to break down new generations of b-lactam antibiotics. These are penicillin and chemically similar derivatives. I am sure that Mr Alesbury would be much more familiar with these things than I am.

It may regain function through mutation or recombination on being transferred horizontally, as was also pointed out by the Government's own scientific advisors in this letter. It is the last paragraph on page 2. It says here:

> "The bla_{Tem} gene has been used in the construction of some transgenic plants."

The nomenclature is very confusing. This is possibly the same gene that is in the pUC18. It is the same as the *AmpR* gene. It says:

> "The parental gene encodes a narrow spectrum b-lactamase that confers resistance to penicillins such as ampicillin and to certain of the older cephalosporins. The gene encoding this b-lactamase undergoes mutations that alter its active site, the consequence of which is to extend the spectrum of activity of the enzyme. This leads to a phenotype that includes resistance to the newer

> cephalosporins; drugs that are commonly used to treat life-threatening Gram-negative infections."

Gram negative is just a major classification of bacteria, as either gram negative or gram positive:

> "Alternatively, mutations in this gene mean that the enzyme is no longer susceptible to inhibition by agents such as clavulanic acid, used to overcome the resistance phenotype. If passage of the gene through a transgenic plants lead to alteration of the codon usage, as acknowledged in the document [from the US FDA], then the possibility that the phenotype may be extended should also be considered."

Maybe I should explain the 'codon usage'. What happens is that, in order to make the gene, the antibiotic resistance gene active in the plants, they have to alter the sequence of the gene in such a way that it is recognised by the plant's machinery for translating it into protein. Part of the machinery is that the codons used are different. The codons are the triplets of bases [letters] that each code for a different amino acid -- there are 20 different amino acids and triplets of four letters, as I said, A C, T, G make 64 possible codons. So there is a measure of redundancy. You can tell that more than one codon codes for each amino acid. This is where the codon usage probably comes from.

Basically, what the scientist is saying is that the DNA that is put in, this antibiotic resistance gene, even though it has been altered so that it is used now more by the plant, recognised more by the plant, it can still back-mutate to be recognised by bacteria. Because this gene is inherently very mutable, regardless of any new generation antibiotic you throw at it, it can mutate to disable the new antibiotic. Any new inhibitor that you throw at it to try to inhibit the enzyme that breaks down the antibiotic, again, it may be able to overcome it by mutation.

I know it is rather complicated.

There is an entire class of transposons in bacteria, which constitutes another danger, even though this *AmpR* gene in Chardon LL does not have a promoter any more. Geneticists have discovered a whole class of transposons -- these are jumping genes remember -- called integrons, that can take up an antibiotic resistance gene and provide it with a ready-made promoter. In other words, this integron has places for slotting in antibiotic resistance genes without promoters, because they have a promoter in front of them so that they can be expressed.

MR ALESBURY: Can I just remind you to take it at a slightly more measured pace for the transcript, particularly when you are on the various insertions and bits you are adding to the written text. It makes things very difficult, I think.

MAE WAN HO: We have drawn attention to it in I-SIS's written objection.

It should also be noted that if there is a rearrangement of the GM construct, which brings the CaMV 35S promoter next to the inactive ampicillin resistance gene, that will restore gene expression because the CaMV 35S promoter is actually functional in bacteria.

As we said before, the fact that the CaMV 35S promoter has a recombination hotspot means that this can take place, this may take place; it is a possibility that should not be ruled out.

Hazards from horizontal gene transfer. The hazards from horizontal gene transfer of GM constructs such as that in Chardon LL, are summarised as follows:

new viruses that cause diseases due to recombination between viral genes and viruses in the environment.

Now, this is not a theoretical possibility any more because recombinant infectious viruses have been recovered in many GM plants containing GM virus genes that are supposed to make the plants resistant to viral infections. This is reviewed in a document that I brought here, BG/1G. It is on page 2, the second last paragraph:

> "It is also clear that recombination between viral transgenes..." (GM viral genes that are in GM construct) "and infecting viruses can occur. A number of studies have demonstrated that plant viruses can acquire a variety of viral genes from transgenic plants. It indicates that viral transgene isolated from the virus and integrated in the host genome cannot be equated with the same gene in the virus itself."

Then it goes on in the next paragraph to summarise all the examples of recombination between GM genes containing viral genes, the viral genes in the GM construct and viruses that infect the GM plants -- which I shall not read out for the sake of saving time.

The next bullet point [on hazards from horizontal gene transfer of GM constructs]: "new bacteria that cause diseases due to recombination between bacterial genes and bacteria in the environment." We have no direct evidence for this, basically, because no experiments have been done. But as we all know, absence of evidence is not evidence of absence.

The existence of uncharacterised sequences from the bacterial plasmid vector in Chardon LL is particularly relevant here. Basically, because these [plasmid vectors] have bacterial origins, they are mixed. They have parts originating in the parasites of different bacterium. If you put them out into the environment, as I have said before, sequences that are similar, that show [phylogenetic] relationships, tend to recombine much more readily.

The third bullet point: "spread of drug and antibiotic resistance genes to bacteria, making infections much more difficult to treat" As I have already summarised, the transfer of antibiotic resistance genes from GM plant material to soil bacteria in fungi has been found both in the laboratory and in the field. There is no reason to expect that Chardon LL's ampicillin resistance gene will not be transferred.

"Harmful effects, including cancer, as the result of random insertion of GM constructs into cells." This possibility is amply demonstrated in gene therapy experiments, where similar constructs are introduced into cells in tissue culture. In tissue culture cells, you very often get cells that become cancerous when they receive such vectors. Of course, I drew attention earlier to a lot of evidence of so-called insertion mutagenesis, and in certain cases, carcinogenesis, associated with many types of cancers, which are due to the integration of foreign genetic material.

The next bullet point: "dormant viruses reactivated by the Cauliflower Mosaic Virus and other viral promoters." Recombinant replicating viruses routinely arise when gene therapy vectors are 'packaged' in cultured cells that contain dormant viruses. I have already drawn

attention to that earlier.

Finally, "multiplication of ecological impacts due to all of the above".

Do not forget that these not only affect human beings, but also mammals, birds, fish, everything; because those GM constructs are going to pollute the environment in general, not only in our air, but in the water, in the soil.

There is now overwhelming evidence that horizontal gene transfer and recombination are responsible for the resurgence of drug and antibiotic resistant infectious diseases worldwide within the past 25 years.

I now refer to the attachment, BG/1M. It is a comprehensive review entitled, "Gene technology and gene ecology of infectious diseases", co-authored by myself, together with six other scientists. I can read them out.

MR ALESBURY: You do not need to.

MAE WAN HO: It was published in the journal *Microbial Ecology in Health and Disease* in 1998, volume 10, pages 33 to 59. We reviewed the evidence extensively, and questioned whether genetic engineering, in enhancing horizontal gene transfer and recombination, may have contributed, and will continue to do so, to the resurgence of drug and antibiotic resistant diseases, if unchecked.

I would like to draw attention to page 54, section 12, conclusions, where we have provided a list of inductive, deductive and circumstantial evidence on why we think this needs a comprehensive public inquiry. Perhaps in the interests of economy of time, I shall not read them out, but there are ten items under inductive evidence, four items under deducted evidence and two under circumstantial.

We have challenged the people who disagree with us in the scientific community to reply to those points, but they have yet to do so.

I would like to read out the final paragraph in our conclusion:

"The totality of evidence is sufficiently compelling, especially in view of the precautionary principle, to warrant, at the very least, an independent, full public inquiry into genetic engineering biotechnology and the etiology..." (meaning causation) "of infectious diseases. In addition, we urgently need research directed at understanding general mechanisms for horizontal gene transfer, which aim to strengthen the barriers against the transfer of recombinant DNA" (these are GM constructs) "and which can form the basis for scientific risk assessment."

The point is that there is not enough scientific knowledge for really informed scientific risk assessment:

> "Such research must be carried out by independent research groups dedicated to the task, and not left in the hands of those who are involved in commercial exploitation of genetic engineering biotechnology."

I reiterate: the current regulatory systems do not take horizontal gene transfer into account. There is no requirement for industry to monitor and report on horizontal gene transfer. On the contrary, dangerous vectors, GM constructs and GM genetic material are either being released directly into the environment or are being recycled as food, feed, fertiliser and landfills.

We have (by 'we' I mean scientists, including myself) repeatedly drawn attention to the dangers of horizontal gene transfer to no avail. Our Government, as well as the biotech companies, have been acting in violation of the precautionary principle as well as sound science. Governments as much as the biotech companies may well be held legally responsible for any harm from GMOs.

I have to tell you that there have been already several lawsuits in the United States against the United States Government for releasing GMOs without proper safety assessment, without environmental impact assessments, and so on.

The version of the precautionary principle most relevant for GMOs is one stating that when there is reasonable suspicion of serious irreversible harm, lack of scientific certainty or consensus must not be used to postpone preventative action.

Here, I would like to stress irreversible harm, because the genetic material, GM genetic material, once you release them out into the environment, will be transferred both to related species and to unrelated species. They will get amplified, or multiplied. They will continue to mutate. They will recombine and you cannot control them.

Furthermore, there is certainly no scientific consensus [on safety], as evidenced by the hundreds of scientists who have signed our World Scientist Open Letter, but there is a deeper point here which I would like to talk about.

I hold that the precautionary principle is part and parcel of sound science because science, as opposed to fundamentalist religion, is an active knowledge system, because some religions are not fundamentalist and they actually are active as well. It is an active knowledge system. Scientific evidence is always uncertain and incomplete because it is active.

The proper role of science and scientific evidence is to provide the grounds for making decisions based on the precautionary principle. It is to set precaution. Dr Peter Saunders, Professor of Applied Mathematics and co-founder of ISIS, in this document that is presented as supporting evidence, BG/1B, on page 14, [wrote the article] "Use and abuse of the precautionary principle". I recommend everyone to read it. Let me just try to summarise what it says.

Basically, he shows how the precautionary principle is just codified common sense that people have accepted in courts of law, as much as statisticians have accepted in setting the burden of proof. Society accepts, with the law, that a person is assumed innocent until proven guilty, beyond reasonable doubt, because, so the saying goes, it is better that a hundred guilty men should go free than one innocent man should be convicted, because it is considered so terrible to send an innocent man or woman to the gallows or to prison, to ruin

an innocent life in this way.

If we seriously want to protect health in the environment, then we must acknowledge that there is already reasonable suspicion that GM technology is hazardous and that the effects are uncontrollable and irreversible. The burden of proof, therefore, should be on industry to establish it is safe beyond reasonable doubt, particularly as there is no evidence of benefit or need. I shall go to that later. Unfortunately, our regulatory systems have operated the other way round. The burden of proof is on civil society to establish it is harmful before it can be rejected.

Crudely, it says, we have to count the bodies first. It means that, in the case of Thalidomide, we had to wait until 8,000 babies were born without limbs before we can say there is scientific evidence that Thalidomide is harmful.

Now, that kind of science, if you excuse my saying so, is completely useless. We do not want that kind of science.

Statisticians have actually been practising precaution by setting what they call the 5 per cent probability as the level of significance. What does it mean? It means that to justify introducing something new, one should assume a "null hypothesis", that there is no difference between the old and the new, unless the improvement observed is such that there is only a 1 in 20 chance for getting the observed difference. 1 in 20 is a small probability.

The same goes for safety testing, although you may think, well, maybe we should be even more cautious about the safety of something which is completely new, but never mind, okay, we should say we start with null hypothesis, that there is no difference between GM and non-GM. However, the failure to show that GM is significantly harmful does not mean it proves GM is safe, because many factors can contribute to this failure to show it is harmful, including insufficient number of experiments and experiments which are badly designed and executed. Unfortunately, such failures have all too often been taken as evidence that GM is safe.

Let me refer to the article itself to give two out of many possible examples that could be referred to.

It is page 16 in BG/1B. I shall begin with the first full paragraph:

"Suppose we obtain a p value."

Sorry, maybe I should just explain. Professor Saunders used the example of an antique coin; obviously antique coins are not very well made so it could very well be biased. In an unbiased coin, if you throw it up in the air, there should be a 50:50 chance that it lands head or tail upwards. Unfortunately, if you have an antique coin, it could very well be biased. So someone has an antique coin that he assumes is biased, and he tosses it three times and it comes up heads all three times, he says, "Oh, you know, that is suspicious". Then someone who claims to know about statistics comes along and says, "What is the probability of getting heads three times in a row?" The first toss is 0.5, the second toss is another 0.5, and the third is another 0.5. So, to get the aggregate probability, you multiply 0.5 x 0.5 x 0.5, in

which you get 0.125. This is way larger than 5 per cent. So he said, "No, you do not have to worry. It is not significant."

Now, this is obviously a case where the experiment is limited because they have failed to prove that the coin is biased, but that does not mean that it proved the coin is unbiased.

I start reading on page 16 from the third paragraph:

"In the example of the antique coin, the null hypothesis was that the coin was fair. If that were the case, then the probability of a head on any one throw would be 0.5; so that the probability of three heads in a row would be 0.5 cubed, which equals 0.125. This is greater than 0.5, so we cannot reject the null hypothesis. Thus, we cannot claim that our experiment has shown the coin to be biased. Up to that point the reasoning was correct. Where it went wrong was in the claim that the experiment had shown the coin to be fair. It did no such thing. Yet that is precisely the sort of argument that we see in scientific papers defending genetic engineering.

"A recent report," which I have already drawn attention to, ""Absence of toxicity of the Bacillus thuringiensis pollen to black swallowtails", claims, by its title, to have shown that there is no harmful effect. In the discussion, however, the authors state only that there were no significant weight differences among larvae as a function of distance from the cornfield of pollen level. In other words, they have only failed to demonstrate that there is a harmful effect. They have not proven that there is none."

Actually if you look at the paper itself there are many faults with the experimental design, with execution of the experiments which, as I say, is not a good experiment.

"A second paper claims to show that transgenes in wheat are stably inherited. The evidence for this is that the transmission ratios were shown to be Mendelian in eight out of 12 lines." This paper is cited. I would like to draw attention to it, although I do not have it with me here. It is published by Cannell et al in *Theoretical and Applied Genetics*, volume 99, in 1999, pages 772- 784.

"In the accompanying table, however, six of the p values are less than 0.5 and one is 0.1. That is not sufficient to prove that the genes are unstable and so inherited in a non-Mendelian way." ‘Mendelian’ comes from the geneticist Mendel who invented genetics:

"But it does not prove they are" (that they are stable) "which is what was claimed.

> "The way to decide if the antique coin is biased is to toss it more times and see what happens. In the case of the safety and stability of GM crops, more and better experiments should be carried out."

Finally, what I want to say is that we should reject not only Chardon LL, but the whole GM approach, at least in its present form. The scientific evidence of actual and suspected hazards arising from GM technology is sufficiently compelling for hundreds of scientists around the world to call for an immediate moratorium on further environmental releases, in accordance with the precautionary principle as well as sound science.

The scientists also demand a ban on patents on life-forms and living processes on grounds that they amount to corporate ownership of life that destroy livelihoods, compromise food security, violate basic human rights and dignity and are contrary to public good. I have no time to go into this in detail, but all of this is argued in our World Scientists Open Letter [BG/1A].

Supporters of GM agriculture are still speaking of potential benefits after more than 20 years, because there has been none so far. Evidence is emerging that GM crops are agronomically as well as ecologically unsustainable. Transgene instability due to gene silences, rearrangement and loss of GM constructs gives rise to inconsistent performance in the field, yield drag and other failures. There is no evidence that Chardon LL will be different.

I draw attention to the supporting document, BG/1A, paragraph 3, page 3:

> "Two simple characteristics account for nearly the 40 million bacteria of GM crops planted in 1999. Of the majority, 74 per cent are tolerant to wide spectrum herbicide with companies engineering plants to be tolerant to their own brand of herbicide, whilst most of the rest are engineered with Bt toxins to kill insect pests.
>
> "A university based survey of 8,200 field trials of the most widely grown GM crops, herbicide tolerant soya beans, reveal that they yield 6.7 per cent less and require 2-5 times more herbicides than non-GM varieties. This has been confirmed by a more recent study in the University of Nebraska:
>
> "Yet other problems have been identified: erratic performance, disease susceptibility, fruit abortion and poor economic returns to farmers."

Again, paragraph 17, page 7:

> "The instability of transgenic DNA in GM plants is well-known. GM genes are often silenced but loss of part or all of the transgenic DNA also occurs, even during later generations of propagation. We are aware of no published evidence for the long-term stability of GM inserts in terms of structure or location in the plant genome in any of the GM lines already commercialized or undergoing field trials."

This must be provided in the case of Chardon LL as well as for other GM crops.

Global market for GM crops has collapsed, as people all over the world are rejecting them and opting for sustainable organic agriculture. Agro-ecological approaches since the 1980s, which combine local farming knowledge and techniques with contemporary western scientific knowledge, have led to improved yield, as well as social economic, health and environmental benefits for tens of millions in the developing as well as the developed world.

I draw attention to the same documents, paragraph 27 and 28 on page 9:

> "Successive studies have documented the productivity and sustainability of family farming in the third world as well as in the north."

This footnote refers to Jules Pretty, a very useful book, published in 1995, *Sustainable agriculture,* Earthscans, also Jules Pretty, 1998, *The living land: agriculture, food and community regeneration in rural Europe*, also Earthscan, in London:

> "Evidence from both north and south indicates that small farms are more productive and more efficient and contribute more to economic development than large farms. Small farmers also tend to make better uses of natural resources, conserving biodiversity and safeguarding the sustainability of agricultural production."

In the footnote, it refers to a report by Peter Rossett, 1999, *The multiple functions and benefits of small farm agriculture in the context of global trade negotiations*, the Institute for Food and Development Policy, policy brief number 4:

> "Cuba responded to the economic crisis precipitated by the break-up of the Soviet bloc in 1999 by converting from conventional large scale, high input monoculture to small organic and semi-organic farming, thereby doubling food production with half the previous input."

Note 60--

MR ALESBURY: There is no need to read it out, if you are just going to read the footnote. I can see that.

MAE WAN HO: [Paragraph]28:

> "Agro-ecological approaches hold great promise for sustainable agriculture in developing countries, in combining local farming knowledge and techniques, adjusted to local conditions, with contemporary western scientific knowledge. The yields have doubled and tripled and are still increasing. An estimated 12.5 million hectares worldwide are already successfully farmed in this way. It is environmentally sound and affordable for small farmers. It recovers farming land marginalised by conventional intensive farming. It offers the only practical way of restoring agricultural land degraded by conventional agronomic practices. Most of all, it empowers small family farmers to combat poverty and hunger."

My conclusion is that we should reject not only Chardon LL but the entire genetic modification approach based on a discredited, mechanistic paradigm. I have no time to go into, but it is actually published in my book that somebody has already given you a copy of. This paradigm is at odds both with the scientific findings of the new genetics and with our aspiration for a safe, healthy, just and compassionate world. Thank you very much.

MR ALESBURY: That was extremely interesting and helpful. That reference 28 [in the witness brief] was to your book.

MAE WAN HO: Yes, it was to my book.

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