GMO expertise: assessment turns its back on science

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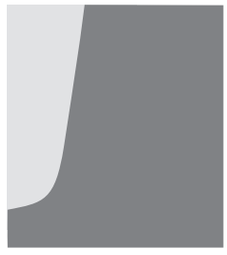

It is essential to emphasize that the issue of GMOs is not limited to the technical aspect. One could even consider this aspect to be absolutely minor. The modern development of biotechnologies (not limited to GMOs) has led to major societal and ethical problems, which must not be dealt with simply by using “scientific” expertise. Nonetheless, the promoters of these technologies, whether they are scientists, engineers or politicians, wax lyrical about Science, Real Science and “sound” Science. Well then, let them really do science, by at least respecting the basic principles of scientific reasoning.

Moreover, and even if once again this does not resolve the issue, far from it, it is normal for genetically modified products grown and/or consumed (1) to be provided with a health and environmental evaluation.

The dossier on Monsanto maize MON810 is not unique with regard to scientific shortfalls, but this maize is currently the only one being grown in the European Union, and is the subject of a ban on cultivation by several Member States. That is why it has been chosen here to serve as a basis for a critical analysis of the health “assessment” of GMPs (2), as it is currently carried out.

In this work, we deliberately kept ourselves out of the scientific controversies which are raging in the field of GMO assessment. We are not trying to adopt a standpoint with regard to whether or not these organisms produce negative effects, nor to say who is right or wrong. The aim is rather to show the limited scope of the tests carried out for evaluations, which must be compared to the firm conclusions made by applicants, and experts in their capacity as experts (not to mention the transcription of these conclusions by certain politicians…) In order to achieve this, we based ourselves essentially on the publications by these same experts, but acting in their capacity as scientists (reports, scientific opinions, publications in scientific journals) or on publications, most of which they had quoted themselves (and which they had thus validated). If, by some miracle, there was a conflict between the scientific presentations and the statements made by experts, it would not be a matter of controversy but of schizophrenia.

A few notions about the evaluation and regulating bodies which are useful for understanding the text.

The Organisation for Economic Cooperation and Development (OECD) is an intergovernmental organization including 34 countries (mainly developed countries) for defining together standards and recommendations on a number of subjects (agriculture, education, development…). It also produces statistics on a global scale.
The FAO (3) and the WHO (4) are two UN institutions, the first specialising in issues of food and agriculture and the second in issues of health. Together, they created the Codex Alimentarius Commission (5), respon-

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1, It must be noted that there are no assessments, not even poorly done ones, for a number of GMOs obtained through mutagenesis and not transgenesis, see: *New manipulation technologies of living organisms* (2012), PEUV ed, Emergence collection. http://www.infogm.org/spip.php?article5191
2, Genetically Modified Plants
3, Food and Agriculture Organisation : http://www.fao.org
4, World Health Organisation : http://www.who.int/en/
5, Inf’OGM's articles on the Codex Alimentarius : http://www.infogm.org/spip.php?rubriques519

sible for developing international standards on food safety, called the Codex Alimentarius, and used as a reference in the context of the World Trade Organisation (WTO). The work of these bodies covers all of the UN Member States (193 States).

The European Food Safety Authority (EFSA) provides risk assessments to the European Union, regarding food and feed safety.

In France, the expert body regarding human and animal health is in the hands of ANSES (French Agency for Food, Environmental and Occupational Health and Safety). Created in 2010, it was created as result of merging AFSSA (French Food Safety Agency) and AFSSET (French Agency for Environmental and Occupational Health and Safety).

Furthermore, in France the government's choices on biotechnologies are guided by the High Council of Biotechnologies (HCB), which issues scientific opinions and recommendations on economic, ethical and social aspects. It was created to replace the Preparatory Committee for the High Authority (in French: CPHA), which itself had succeeded the French Biomolecular Engineering Commission (in French: CGB) and the French Genetic Engineering Commission (in French: CGG) (6).

6, http://www.hautconseildesbiotechnologies.fr/spip.php?article42

1. MON810 maize: a presentation

Originally, Monsanto's project was to create a maize variety which produced an insecticide against corn borer, a moth whose larvae live as parasites in maize, and which was tolerant to its flagship herbicide, Roundup©, whose main active ingredient is glyphosate.

In order to produce it, cultured maize cells were bombarded with minuscule metallic particles coated with two artificial cassettes containing a gene encoding a glyphosate-tolerant enzyme and a gene encoding an insecticide protein from a soil bacterium, *Bacillus thuringiensis*, from which the name "Bt protein" (1) comes. The genetic construction was supposed to stop in the nucleus and integrate itself somewhere on the chromosome level during the passing of the metallic particles to which transgenes were bound. As this of course only occurred for a small number of cells, the operation had to be completed using a system for selecting the cells into which the transgene had been well and truly incorporated.

For the case at hand, because Monsanto was aiming for glyphosate tolerance, after bombardment, the maize cells were grown in an environment containing the herbicide, in order to kill those which had not been transformed. This was how MON810 was selected… For the record, this selection was carried out after a selection protocol deficiency, as in fact, the glyphosate-tolerant gene had not been incorporated. The MON810 cells should have died, killed by the glyphosate, but they survived due to an experimental error: had the glyphosate been forgotten, had there been an error in dosage or had the cells been badly shaken? We will never know.

A protein-coding gene (a DNA sequence) is at the very least made up of a promoter, which allows the gene to be expressed, an actual coding sequence, and finally, a small "terminator" sequence, which marks the end of the "reading" (in other words the transcription).

In the case of MON810, the transgene coding the Bt protein, an insecticide, was only incorporated into the maize chromosome very incompletely. The insert (transgene) was in fact only made up of the last part of the promoter and only one part of the coding sequence. As regards the terminator, it was purely and simply lost along the way, which means that during transcription, it was the genome of the maize adjacent to the transgene which was read. For MON810, this resulted in the production of one hybrid protein (perhaps two, we do not know) (made up of one piece of the Bt bacterial protein sequence and one piece deriving from the maize sequence, the whole being called "CS-Cry1Ab^{Mon810}" to distinguish it from the original Bt (Cry1Ab) protein. This shoddy workmanship is far from surgical mastery, which is often how this high-tech technology is presented.

Another surprise: the insecticide protein(s) expressed by MON810 not only kill(s) corn borer, but Sesamia as well, another moth pest of maize, resilient to natural Bt protein (Cry1Ab).

Although this concerns a hybrid and truncated protein with different biological properties, we will see that evaluation is based on… the claimed identity of the recombinant protein (produced by the maize) and the natural bacterial protein. Nothing but sound science.

1, There are several classes of Bt proteins. For MON810, it is a CRY1Ab. See annex 1: Bt proteins, p.45

The accuracy of the data provided by Monsanto in the authorisation dossier can be judged by this extract quoting HCB's opinion, in which, after warning that the case did not contain any experiment allowing one to know whether one or two recombinant proteins (encoded by the transgene) were expressed, it stated that *"nonetheless, one or both proteins are expressed in MON810 and at least one (or both) of them perform(s) an expected action on certain invertebrates given that this plant is resistant to corn borer"* (2). Therefore, we are not entirely sure what this shoddy workmanship really produces, but it kills corn borer (and even Sesamia): what more could one ask for?

2, Monsanto SA, *Application for renewal of the authorization for continued marketing of existing MON810 maize products*, mai 2007, 27 p.

2. The assessment conditions

Dossiers, whether for consumer food products or cultivation, in principle follow guidelines laid down by the European Commission, which are themselves based on OECD protocols (1). These guidelines are not binding. These dossiers are drafted by the applicant (for MON810: Monsanto) based on analyses carried out by laboratories which are paid directly by the applicant. As the CEES of the HCB (2) underlines, the applicant *"is judge and judged"* (3). Under these conditions, evaluation bodies (EFSA (4) for the European Union for example) must trust the applicant. As they do not have the time, funds or equipment necessary, they cannot actually carry out the analyses themselves and can only read the dossier presented, as well as the scientific literature on the subject. Such practices imply that the applicant must be perfectly fair when providing data, their account and their analysis. It goes without saying of course that if this fairness were undermined, then trust could no longer be placed in them and the dossier would have to be rejected, given its incredibility. However, this is not the attitude adopted by the bodies of expertise, in particular regarding MON810, as will be shown hereafter. Moreover, some experts adopt fallacious arguments as their own..

2.1. The inappropriate identification of the insecticide protein MON810 as being the natural protein

There are many "Bt" proteins (see annex 1, p.47). The bacterial source gene used to produce the MON810 transgene is derived from a "Bt" protein called Cry1Ab. As we saw, the protein actually produced by MON810 differs considerably and is called CS-Cry1Ab^{MON810}, and the data provided does not allow one to know whether there are one or two structurally different proteins. In its dossier, in order to support the idea that "the" protein produced by MON810 has no impact on health, Monsanto assimilated it to the natural Cry1Ab protein: *"the [Cry1Ab] protein has a demonstrated history of safe use"*, a claim which would be repeated by experts. Not only are these proteins distinct from one another at the molecular level, but CS-Cry1Ab^{MON810} is produced by an eukaryotic organism and not by a bacterium. Its production method is very different from bacterial production and its use in organic agriculture (5) is not comparable to that of a plant which continuously, or almost continuously, produces its insecticide protein in its cells, excreting them through the roots.

2.2. Compositional analyses

Compositional analyses consist of comparing different parameters (composition in terms of amino acids, fatty acids and fibers, etc.) between MON810 and a semi-isogenic maize, in other words one with a similar genetic background but without the transgene. Normally, for interpretation purposes, the comparison must be made using both types of maize grown at the same time, under conditions which are as similar as possible so that any existing differences linked to the presence of the transgene appear, and are not confused with differences linked to growing conditions. Essentially, efforts must be made to ensure everything is identical, except the transgene, so that differences stand out and are linked to the transgene. Making growing conditions uniform also means parameter variations are reduced and thus make it easier to see differences, if they exist.

1, Organisation for Economic Cooperation and Development
2, Economic, ethical and social committee of the French High Council of Biotechnologies (HCB).
3, http://www.hautconseildesbiotechnoligies.fr/IMG/pdf/091222_Mais_MON810_Recommandation_CEES_HCB.pdf
4, European Food Safety Authority, EFSA
5, Natural Bt proteins are quickly destroyed by the sun's ultra-violet rays.

Comparing the data of one experiment with data previously published on experiments carried out under different conditions (6) is thus not an acceptable method. However, this is what applicants do and what toxicology experts validate…

Another basic rule is to not select data. In fact, if one only takes into account the data which support the expected conclusion, whilst ignoring any other, one will inevitably end up with what one wants to show. The enormity of this practice is such that it is hard for us to believe that it is not only used by the applicants, but that it is also validated by EFSA and the experts of national committees! This means that on the one hand, if a difference between the GMO and the non-transgenic control specimen is discovered, the applicant looks to see if the GMO's average values fall within the range of data published in other experiments. On the other hand, and conversely, if there is no significant difference, these published data are not used, even if the average falls outside the range of the data. Indeed, nothing but good science!

In this case Monsanto uses two references: the "literature range" (7) and the "reported range" (8). This comparison of the composition of MON810 with a control maize line, in this case MON181, not genetically modified, gives a particularly flagrant example of the applicant's determination to present the data in a favourable light.

The "literature range" comes from a 1982 publication (9) compiled with data on maize grains analyses published at the time. There are data dating back to 1946, other data from crops cultivated in Canada, and all using different varieties and technical analyses which are not exactly identical to those used today. In this publication, the author notes that *"some of the ranges include values for unusual types of corn"* and he specifies, with regard to amino acid analyses: *"values presented by various authors show considerable disagreement"*.

The "reported range" comes from a 1995 report by Monsanto comparing the composition of MON800 maize (non GM) and MON801 (GM). The values used as a reference for MON810 are those of MON800. It is a compilation of crops in five locations in the United States.

For each parameter (alanine, histidine, calcium, etc.) the averages obtained for MON810 are compared to a normal MON818 control plant using a statistical test. If there are no significant differences between both types of maize, the applicant considers that everything is OK. If there is a significant difference, (for example, in the alanine, cysteine or calcium, etc.) the applicant tries to not take these differences into consideration, "justifying" them with ad hoc comparisons to the "literature" and "reported" values defined above.

The comment made with regard to the amino acid composition reads:
"The values for all amino acids were typical of the values reported in the literature (Watson, 1982) and for a control maize line with a similar genetic background (Sanders and Patzer, 1995)".

A simple reading of table 1 (below) shows eight significant difference which are marked as such on the table (by an asterisk), in other words 44% of the values obtained. The averages for MON810 are outside the literature range (three cases) and the reported range (10 out of 18 cases). Monsanto's claim is therefore simply

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6, Comparisons made using "reported data" and "litterature data"
7, Watson, limited company, (1982) "Corn: Amaizing Maize. General Properties" P.3-29 in CRC *handbook of processing and utilization in agriculture*, volume II. CRC Press, Florida
8, Sanders, P.R., Patzer, S.S., (1995) *Compositional analyses of MON 810 grain and silage from 1994 corn field trials*. Monsanto Technical Repost, MSL 14180
9, Watson, limited company, (1982), op. cit. "Corn: Amaizing Maize.

Table 1 Compositional analysis of MON 810 compared to control - 1994 U.S. field trials - continued

	MON 810		Control (MON 818)			
Tissue/Component	Mean[d]	Range[e]	Mean[d]	Range[e]	Literature range[b]	Reported range[c]
Grain– continued						
Amino acids[a]						
Alanine	8.2*	7.8-8.9	7.8	7.5-8.0	6.4-9.9	7.8-8.1
Arginine	4.5	4.1-4.7	4.5	4.2-4.7	2.9-5.9	4.4-5.0
Aspartic acid	7.1	6.4-8.2	6.6	6.3-6.8	5.8-7.2	6.8-7.3
Cystine	2.0*	1.9-2.1	1.9	1.8-2.0	1.2-1.6	1.9-2.3
Glutamic acid	21.9	20.4-24.4	21.1	20.1-21.6	12.4-19.6	19.9-20.9
Glycine	3.7	3.4-4.0	3.7	3.5-3.8	2.6-4.7	3.9-4.2
Histidine	3.1*	2.9-3.3	2.9	2.8-3.0	2.0-2.8	3.0-3.3
Isoleucine	3.7	3.3-4.1	3.8	3.6-4.0	2.6-4.0	3.7-3.8
Leucine	15.0	14.1-16.7	14.5	13.8-15.0	7.8-15.2	13.6-13.8
Lysine	2.8	2.5-2.9	2.8	2.7-2.9	2.0-3.8	2.9-3.4
Methionine	1.7	1.6-1.9	1.7	1.6-1.7	1.0-2.1	2.0-2.6
Phenylalanine	5.6*	5.4-6.1	5.4	5.2-5.6	2.9-5.7	5.2-5.4
Proline	9.9*	9.7-10.5	9.6	9.4-9.8	6.6-10.3	9.0-9.4
Serine	5.5*	5.3-5.9	5.2	5.1-5.4	4.2-5.5	5.5-6.0
Threonine	3.9	3.7-4.4	3.8	3.7-3.9	2.9-3.9	4.0-4.2
Tryptophan	0.6*	0.5-0.7	0.6	0.4-0.6	0.5-1.2	0.5-0.6
Tyrosine	4.4*	4.1-4.8	4.0	3.9-4.1	2.9-4.7	3.8-4.3
Valine	4.5	4.1-4.9	4.6	4.3-4.8	2.1-5.2	4.5-4.8

* Statistical significant differences between MON 810 and control in a paired t-test analysis at the 95% confidence level
[a] Values are expressed as percent of total protein.
[b] (Watson, 1982). Values are percent of total protein [10.1% total protein (Nx6.25)]
[c] (Sanders and Patzer, 1995), range for a control with similar genetic background .
[d] Value reported is mean of six samples, one from each field site (Sanders, 1995)
[e] Ranges denotes the lowest and highest individual values across sites for each line.

Source: Monsanto, public file.
The values are marked with an * where there is a statistically significant difference between MON810/control line.

With regard to the fiber values, it states (table 2. see p.10):
"Crude fiber values in MON810 grain (2.6%) were statistically different than MON818 values (2.4%) but the values are within the range reported in the literature (2.0 – 5.5%)".

The ad hoc nature of the argument here is particularly flagrant: Monsanto notices a significant difference, which is very irritating. Therefore, it looks to see if the average falls within the literature range, which is the case. As a result it concludes that there is no problem. But it does not make any more mention of reported ranges, with the MON810 average of 2.6% being higher than the highest value (2.4%) for the reported ranges.

For phytic acid (table 2), it states:
"There were no statistically significant differences between the values for MON810, and the control MON818, for phytic acid".

In this case, as there was no significant difference, the applicant does not point out that this value was also outside the reported ranges, a reference which is only used when it is in Monsanto's interest.

Then comes calcium (table 2), concerning which they will have to justify a significant difference:
"Calcium was statistically significantly higher in MON810 compared to the control, although the differences are minor (0.0036% compared to 0.0033%). These values are within the range reported for another control maize (0.0030-0.0039%) of similar genetic background (Sanders and Patzer 1995)".

But in this case, the values are from a range of published values…which become, as if by magic, devoid of any informative

Table 2 Compositional analysis of MON 810 compared to control - 1994 U.S. field trials - continued

	MON 810		Control (MON 818)			
Tissue/Component	**Mean[b]**	**Range[c]**	**Mean[b]**	**Range[c]**	**Literature range[d]**	**Reported range[e]**
Grain – continued						
Fiber [a]						
Crude fiber	2.6*	2.5-2.8	2.4	2.3-2.5	2.0-5.5	2.1-2.4
Anti-nutrient[a]						
Phytic acid	0.86	0.81-0.91	0.84	0.80-0.91	0.7-1.0	0.45-0.56
Minerals[a]						
Calcium	0.0036*	0.003-0.004	0.0033	0.003-0.004	0.01-0.1	0.003-0.004
Phosphorus	0.358	0.334-0.377	0.348	0.327-0.363	0.26	0.311-0.356

* Statistical significant differences between MON 810 and control in a paired t-test analysis at the 95% confidence level
[a] Values on a dry weight basis.
[b] Values presented are means of six samples, one from for each field site.
[c] Range denotes the lowest and highest individual value across sites for each line.
[d] (Watson, 1982).
[e] (Sanders and Patzer, 1995), range for a control with similar genetic background.

Source: Monsanto, public file
The values are marked with an * where there is a statistically significant difference between MON810/control line.

What is even more astonishing is that when Monsanto writes the summary of this study, concerning the composition of MON810, miraculously, ALL the values fall within the “literature” and “reported” ranges, whereas we have just seen the opposite:
*“In summary, compositional data for protein, fat, ash carbohydrates, calories, moisture, amino acids, fatty acids, fiber, anti-nutrient and minerals for MON810 was comparable to the control, MON818, and **within published and reported literature ranges for commercial hybrids** (10).”*

In this case, as was the case for the food suitability study for that matter, the argument is ad hoc given that only the data which suits the applicant is used.

Only choosing the data, out of a series of data, which go along with the desired conclusion is an unacceptable scientific practice. Nonetheless it is from this discussion, with no scientific argument, that the conclusion is drawn:
“Based on these data, it was concluded that the grain from MON810 and the control, MON818 are similar in composition and representative of maize grain currently in commerce.”

Then, “similar” becomes “substantially equivalent” (11) and “not different”:
“MON810 has been shown to be substantially equivalent to the non-transgenic controls as well as to commercially available varieties, except for the introduced DNA sequences and the expressed protein. Therefore, when MON810 is used on a commercial scale as a source of food or feed, then these products are not different from the equivalent foods and feed originating from conventional maize.”

Which, with no further argument, ends up being, …”identical”!:
“It is concluded that MON810 is as safe and nutritious as conventional maize and that food and feed products that contain, consist of, or are produced from MON810 are as safe and nutritious as their counterparts derived from conventional maize”.

The *“as safe as and as nutritious as”* clearly exceeding all the scope of the data…

The applicant goes even further, speaking about a positive demonstration (12). This would imply the provision of proof based on an inference, that is to say on a logical implication, which has clearly never been the case and then draws conclusions from it for the use of this GMO which, as they are expressed, are not scientifically substantiated:

10, Underlined by us
11, A concept which, according to the rules of the World Trade Organisation, grants the right to put this GMP on the market.
12, The term “demonstrated” is used 27 times, mostly unfoundedly, in this dossier.

"As demonstrated in this renewal application, MON810 is equivalent to conventional maize except for its protection against certain lepidopteran pests, which is a trait of agronomic interest. This maize was shown to be as safe and as nutritious as conventional maize. Therefore, MON810 and derived products from MON810 will be stored, packaged, transported, used and handled in the same manner as current commercial maize varieties, and measures for waste disposal and treatment of MON810 products are the same as those for conventional maize".

There are other similar examples in the MON810 (13) dossier.

These few examples, which is not an exhaustive list of what we find in this dossier and others, clearly show that the applicant is trying to justify at all costs the conclusion according to which its maize is as safe and as nutritious as normal maize, regardless of the results of the analyses. And since MON810 is identical to all other maize, it must be treated in the same way, QED.

Let us repeat that it is not our aim to know whether MON810 maize, or any other, is toxic or whether it has an impact on the environment. The application dossier for authorisation is written and submitted by the applicant. Experts must therefore trust the content of this presentation. Admittedly, asking an industrialist who is trying to put his product on the market to be impartial is a touch naïve, however, when it is clear that this impartiality is missing, naïve is no longer the appropriate word to use.

2.3. Using published and reported data

Let us go back to that comparison between the averages of the results obtained from the GMO studied (MON810) and the data obtained from crops grown in the past, in different places, and even from different varieties (14).

If it is clear that it is not acceptable to use, as Monsanto used in the aforementioned example, only data from the tables which suit the applicant, one must also understand the general fallacious nature of using "reported" comparators.

a – When two groups are compared, it is not done with regard to the range defined by interval limits, but by a calculation which takes into account the variability and distribution of data. If we look at the two sets in figure 1, one represented by A's and the other by B's, we see that both groups are made up of the same value range but that they are obviously not equivalent. Their distribution and the resulting statistical values as averages, standard deviation or variance, are different. This way of comparing data makes no sense from the scientific point of view.

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A  AA   AAAA AAA       A  A
B    B      B  B  BBB B   BBB
```

Figure 1

b – The parameters studied vary according to the climate, soil, varieties and cultural practices, etc. The more the conditions differ, the greater the range of the data will be (and the higher the variance). This is why we must not compare an average obtained from an experiment carried out in a certain place, at a certain time and under certain conditions with a range of data obtained from a different place, at a different time and under different conditions. The absolutely absurd nature of this type of practice appears simply by reading table 1 (p.9) regarding amino acid levels and this time not looking at the averages obtained from MON810, but those from the normal control maize, which serves as a comparison. Let us then compare this normal control

13, Including, page 132: *"fields studies […] have demonstrated that these crops have no adverse effect on biodiversity…"*. A conclusion which is evidently not acceptable based upon such studies.
14, We found detailed and soundly argued criticism of these practices in a recent publication: Antoniou *et al*. *GMO*

specimen with the literature and reported ranges: in ten cases (15) the control is outside the published and/or reported ranges! In the case of histidine, the control average is actually higher than the highest of the literature values and lower than the lowest reported value (see table 1)… If we believed our toxicologists, friends of sound science, the control specimen used to compare with MON810 is thus both abnormally high and abnormally low with regard to the values which they use as references. Amazing! It is even more amazing that all of this was validated by EFSA without anyone flinching.

Better still: for three of the parameters (16), the literature values are outside of the range of reported values and vice versa (there is no value common to both ranges). The conclusion that must be drawn is enlightening: all the control specimen references are abnormal with regard to each other. This kind of science might be True Science, but it seriously lacks consistency.

15, Aspartic acid, cysteine, glutamic acid, histidine, leucine, lysine, methionine, proline, serline, threonine.
16, Glutamic acid, histidine, threodine.

3. 1. Statistical analyses

If we feed a baby rat with feed containing GM maize, it will grow and fatten up. This does not mean we can conclude that the transgene has resulted in the rat's growth. In order to establish causality, at least two groups need to be compared, which are as similar as possible, except in terms of the factor to be studied. In this case, for MON810, toxicity and feed performance compared two groups of rats: one group was given feed containing MON810 and a control group was given food containing quasi isogenic feed, in other words, as we have seen, having practically the same genetic background (the same variety, but non transgenic).

Of course, nothing is perfect and sometimes the groups of rats are not similar for reasons that are unrelated to the experimenter's intentions. However, the conditions under which they are kept and the conditions of the experiment are normally very strict, so as to avoid artificial differences between the groups (temperature, exposure to light, accidental infection, etc.). These very tightly managed growing conditions are also artificial conditions, which are even less representative of reality because they must comply with the requirements of the experiment. All experiments are artificially controlled conditions and their results, with regard to real life, need to be interpreted taking this into account.

Living beings are not machines and despite taking precautions, it is their variability which characterises them. Were they to be subjected to a given influence, all individuals, as similar as they might be, would not react in the same way. Dosages themselves (or other measures) cannot be rigourously reproduced either. This means that in all cases, if we compare two groups of animals, there will be differences. It is therefore necessary to distinguish between differences caused by chance and differences linked to the phenomenon studied. To say that two averages are different does not mean much, as long as we have not shown that these differences are significant. The first tool used to characterise differences observed is the statistical tool. It is only once statistical studies have identified differences which are statistically significant that thought can be given to considering their biological significance, emphasizing that the latter requires an interpretation which is partly subjective. We will come back to this later.

3.1. Sub-chronic toxicity testing

Here we will consider sub-chronic toxicity tests on rats. For 90 days, rats, both males and females, are fed with feed containing 11% or 33% of the GMO (MON810 maize for example), or with feed containing 33% of the control plant (for example, non-GMO maize grains but with a genetic background as similar as possible to the GMO) (1). Different parameters are studied (body weight, organ weight, blood cell count, biochemical dosages, etc.). For each of these parameters and for each GMO percentage, as well as for each gender, comparisons are made between the "test" groups and the "control" groups. The aim is to see if there is a difference which cannot be attributed to chance, for each of the parameters, which would be the sign of an effect of the GMO studied.

3.2. Basic concepts relating to statistical studies carried out in this context

Probability theorists like urns of coloured balls. Let us do the same and imagine an urn containing a very large number of balls, half of which are red, a quarter of them blue and another quarter green. We take a sample from this general population of, for example, 100 balls. If, when we take our sample we make a selection, only taking the green balls (a little bit like Monsanto selecting the data from the tables earlier on), the sample will not be representative of the population in the urn and the results obtained from the sample will not be applicable to the contents of the urn (in this case, the conclusion: *"all the balls in the urn are green"*

1, As in the case of MON810, another group can be added, fed with 33% of commercial varieties of hybrid maize.

would clearly be false). Taking a sample is a decisive stage, which explains the problems with opinion polls in particular (in real cases, the composition of the general population is not known *a priori*). It must be noted that in practice, it is the sample which defines the general population and not the other way around, as is the case of the urn… what remains to be seen is whether this general population is really the one that interests us. For example, which is the general population from which rats are taken for toxicology studies? The answer is not simple, but the interpretation of results depends on it.

Going back to the case of the urn, if we randomly take a first sample of 100 balls, we will have approximately the proportion of colours present in the urn (2). The same can be said if we take a second sample of 100 balls. If we were now to compare these two samples, which were taken from the same population (taken at random from the same population, they are equivalent), there might be differences (which in practice do exist) linked to random fluctuations in the sampling and, in the case of toxicology experiments, to the individual variation of biological parameters. Statistical tests allow us to know, allowing for a certain risk of error, whether the samples can be considered as from the same population, that is to say that the differences observed between the two samples are not statistically significant (they are compatible with the random fluctuations).

When we test the toxicity of a GMO (or of any other product), we take two samples of rats of a certain breed or strain (generally Sprague-Dawley (3)) from a population assumed to be general and we look to see if it is statistically reasonable to think that the "test" sample has been modified by the GMO compared to the "control" sample.

But what is this general population which the samples represent? This question is important given that the experiments' conclusions are extrapolated to this population. Is it the Sprague-Dawley population and if so, is it those from a specific animal house or Sprague-Dawley rats in general? Is it rats in general? Mammals? Living beings?

Some animals are more sensitive to certain substances than others: some species are more so than others, amongst these species, certain breeds are more so than others, amongst these breeds, some individuals are more so than others. To take an example from rats, the pure-strain Long-Evans rat (4) is a thousand times more sensitive to TCDD (5) than Han/Wistar rats (6). Were we to test the toxicity of TCDD on Sprague-Dawley rats for example, we would not be able to generalise, even for all rats. Obviously, even less so for the human species. **This does not mean that these tests have no informative value, of course they do, but we cannot claim the product is safe for the human species as the logical conclusion of the experiments.**

In the context of decision making (which always includes a non-measurable risk), a negative toxicity test is a factor for discussion and not a guarantee of safety.

2, It must be noted that if there is a minute proportion of violet balls in the urn, let us say one out of one hundred thousand, we would have a one in a thousand chance of finding one in a sample of one hundred balls. There are some animals and human populations with rare sensibilities, which would not be represented in the samples tested. If they are present, they are a unique example (therefore, for one gender and one dose…). This poses the particular and difficult problem of atypical data.

3, Sprague-Dawley rats are "outbred", that is to say that they have some genetic variations, contrary to pure "inbred" strains. Nonetheless, they are not as diverse as a natural population. The choice of this type of rat for toxicology experiments will not be discussed here. However, it can be discussed, see for example: Festing, M.F. (1990) "Use of genetically heterogeneous rats and mice in toxicological research: a personal perspective" *Toxicol. Appl. Pharmacol.* 102: 197-204

4, The Long-Evans strain is "inbred", that is to say that this strain of rats are like twins (practically homozygous for every locus) because they have been bred with each other over many generations. Here, a population of these rats behaves like an individual, with regard to the genetically-controlled characteristics.

5, TCDD is a dioxin.

6, Pohjanvirta, R et al. (1999) "Physiological differences in the AH receptor of the most TCDD-susceptible and the most TCDD-resistant rat strains", *Toxicol. Appl. Pharamcol.* , 155: 82 :95

This is a significant nuance and, one which clearly escapes a number of politicians and journalists, as well as researchers!

Direct extrapolations to the human species (or all species) such as those quoted above made by Monsanto *"It is concluded that MON810 is as safe and as nutritious as conventional maize"* are absolutely unacceptable. It is very surprising that this kind of conclusion is used by qualified experts from official "neutral" agencies like EFSA.

Such claims, which clearly go against the rules of scientific procedure, are enough to discredit EFSA. But there are other reasons to discredit it.

3.2.1. Statistical error

When we measure something, there is always inaccuracy, caused by the measuring tool used. When this tool is calibrated, we know that the "real" value falls within a given range. Statistical uncertainty is different in nature. It is not about inaccuracy but rather about the probability of being mistaken when reaching a conclusion, without prejudging the extent of the mistake made (nor the consequences of this mistake).

If the conclusion is *"the different levels of calcium in the blood observed between the group of rats which ate GMOs and the control group of rats is significant to a statistical risk of 5%"*, it means that the difference cannot be attributed to chance (the GMO is causal if the sampling of the rats is really random) with a 5% probability of being mistaken.

If we compare the two samples of rats from the same population and fed in the same way (therefore, identical) and if we compare these two samples, which are equivalent, for one hundred parameters (size, weight, blood sugar, etc.), with a 5% risk, **there will be around five parameters with a significant difference even though these differences are not real (false positives)**. We could reduce the risk of being mistaken, but then we would reduce the probability of highlighting real differences (7). The choice of error rate depends on what we are trying to do. In a toxicology test, where we are trying to research the differences between the groups, we are better off choosing a 5% or even 10% limit, which are high risks, given that it is important not to miss anomalies and thus better to "cast a wide net". This means that, based on other arguments, we must then discuss the biological significance of the differences observed (EFSA recommends using the terms statistically significant and biologically relevant, to distinguish between the nature of these concepts). Because, contrary to what is sometimes put forward by associations or journalists, a statistically significant difference does not imply biological relevance. Statistical data (if they are obtained in accordance with the rules, which as we will see is not the case for GMO authorisation dossiers) are scientific data. Their interpretation, however, comes from expertise, that is to say, from a kind of truth which is different from scientific truth. This difference in status is by no means derogatory. It is just about understanding that the kind of truth is not the same in their relation to the data. On the whole, a toxicology test is a decision support tool and not a scientific demonstration.

However, the fact that a number of significant differences observed are close to the error rate chosen as the significance threshold does not mean that these differences should be ignored. This is an argument which is nevertheless often found in the dossiers, where we often come across sentences such as *"there are about 5% of significant differences, therefore we do not need to take them into account"*.

3.2.2. The power of these tests

There is an enormous difference between doing something imperfect yet useful and acting as if one was doing something (while pretending moreover that it is a demonstration!). It is especially here that we come across scientific fraud, as we will now demonstrate.

7, We would in fact reduce the power of the test (see below).

Stating that nothing is seen is only of interest if one at least looks. Furthermore the adequate means must be used to be able to search for what has to be found. If you put a watchman in a tower to see if the enemy is coming, security is not the same if he is long- or short-sighted. Similarly, if we ask if there is an elephant in the room, we could, providing we looked, be confident about its absence. However, under the same conditions, stating that there is not a particular bacterium because we cannot see it with the naked eye is stupid. Discriminatory power must be adapted to what we are trying to see.

It is the same for statistics: statistical power must be adapted to the importance of the effect which we want to be able to detect. This power is calculated. It is based on the variability of the measurements of the parameter in question and the number of animals used for the test, for a given detection threshold. If this power is not given, the test cannot really be interpreted, given that we do not know whether the watchman is long- or short-sighted.

Let us say straight away, although we will come back to this, that the power of statistical tests used in toxicology or food suitability tests is **NEVER** provided in **ANY** authorisation application for the placing on the market or cultivation of GMOs. This issue, as well as that of using null hypotheses, has been part of a long battle carried out by GIET, with the help of FNE and Inf'OGM, which demonstrates the glaring shortfalls of evaluation (see below).

3.2.3. Null hypotheses: difference or equivalence

When two populations are compared, statistical tests can only do one thing: refute a hypothesis, according to the chosen statistical risk, called a "null hypothesis" and note down "H0". Statistics do not state, they refute.

In our case, toxicology, two hypotheses can be tested:
a – The null hypothesis is *"both groups are identical"*. In our case, this is also expressed as *"the GMO has no effect"* (difference test);
b – The null hypothesis is *"both groups are different"* or *"the GMO has an effect"* (equivalence test).

Given the importance of the wording, it is worth stopping here for a while. If the null hypothesis (a) is rejected, the result is positive: we refute (on the basis of the chosen statistical risk) the identity of both groups (thus, we claim that they are different. This is why the test using this null hypothesis is called the difference test). However, if we cannot reject this same null hypothesis (a), the result, which is negative, does not allow us to state that the groups are identical, but only to claim that we were unable to show that they were different. In fact, with more power, the null hypothesis could have been rejected. If something is seen (in this case, a difference), it exists. If it is not seen, it does not mean that it does not exist, but rather that, under the conditions of the experiment, we did not see it. As is strongly emphasized by EFSA: *"Absence of evidence is not evidence of absence"* (8). It is a pity that EFSA does not listen to its own recommendations… In the case of null hypothesis (b), refuting it implies rejecting the difference of the groups, which are thus claimed as being equivalent, this is the equivalence test.

Difference and equivalence tests follow different protocols, the equivalence test being harder to carry out than the other. This is also the one which is advantageous to the consumer, given that a lack of power would prevent the safety of a GMO being established (for the rats concerned). The applicant is therefore encouraged to carry out powerful and correctly executed tests to prove that the product is safe (for the rats).

In the chapter *"the statistical tool: a decision support tool"*, a Terminale S (French Final High School Science level) statistical manual (9), the example given is the case of GMO evaluation and they interpret these concepts in these terms:

8, *EFSA journal* 2010;8(1):1250 p.17
9, *Statistiques et probabilités in Math'x (Statistics and probabilities) terminale S spécialité –manuel.* Programme 2011. Ed. Didier. It's a manual of statistics for the last high school year in France.

"The real question which should be asked is whether these differences are important enough to be associated with a toxic effect. The appropriate statistical tool to answer this question is not the means comparison test (particularly favourable to industrialists, based on the principle that there is no GMO effect) but the bioequivalence test which protects the consumer better by being based on the hypothesis that there is a worrying GMO effect: it is then up to the experiment to show that this is not the case".

Must we then conclude that EFSA's GMO Panel does not have the same level of education as a last year high school student?

The problem is that this equivalence test is NEVER carried out for GMOs.

Furthermore, claiming an equivalence or identity between the groups means that equivalence tests would have had to have been carried out. This is obvious, but it is specifically remembered and underlined in ANSES' opinion with regard to statistical tests carried out in the toxicology study on GMOs (10):
"The study's conclusions which use the term "equivalent between the two sets" must be justified using equivalence tests".

Yet, claims of equivalence are regularly given in the dossiers (including for MON810) without any equivalence test ever having been carried out.

These inconsistencies are regularly criticized by the HCB in its opinions. For example, in the dossiers on the genetically modified maize MIR604 made by Syngenta, the HCB is particularly explicit. When the applicant declares: *"These findings support the conclusion that grain and forage from MIR604 maize are compositionally equivalent to the conventional maize varieties except for the presence of the newly introduced intended traits"*, the HCB replies: *"the comparison tests do not allow to conclude there is equivalence: an equivalence test should have been carried out in order to reach this conclusion"* this comment is repeated every time Syngenta claims there is equivalence, particularly when the company concludes: *"Therefore it can be concluded that MIR604 maize is as nutritionally wholesome and equivalent to conventional maize"*, a strong conclusion but which has no scientific basis.

In the case of MON810, Monsanto did not hesitate to claim: *"No specific conditions are considered necessary for the placing on the market of MON810.* ***As demonstrated*** *in this renewal application, MON810 is* ***equivalent*** *to conventional maize except for its protection against certain lepidopteran pests."*

What is even more serious is that EFSA itself writes, in the conclusion of its 2009 opinion on MON810:
"…maize MON810 is as safe as its conventional counterpart with respect to potential effects on human and animal health" (11).

As we have seen, not only can extrapolating the data obtained from rats to humans not be done this way, but this can even be said for rats and specifically for Sprague-Dawley rats, where the tests carried out do not allow to confirm equivalence between the test and control groups.

This inadmissible conclusion only uses the previously drawn conclusions about MON810 or other GMOs. This led the GIET, then helped by FNE and Inf'OGM, to try and obtain clear answers from EFSA and to force the European Commission to clean up this situation. This affair will therefore be recounted in chronological order.

10, ANSES (2011) "Recommendations for carrying out the statistical analysis of data from sub-chronic toxicity studies of 90 days on rats in the context of an application for authorisation to put the GMO on the market". In French (http://www.anses.fr/index.htm).
11, *EFSA journal* (2009) 1149 :1-84

4. The MON810 affair

MON810 maize was authorised for cultivation in the European Union in 1998 for ten years. After these ten years, as an authorisation renewal was needed, Monsanto filed for an extension. Once the authorisation deadline has passed (after the first ten years), and if the authorisation renewal application has been made, authorisation remains valid as long as the European Commission has not given a ruling on renewal (in accordance with Article 17.9 of Directive 2001/18).

In 2007, the application for renewing MON810 was referred to the CGB. The work started in Parma with EFSA and a few members chosen by the CGB, without the other members taking part in the work. The CBG's mandate expired at the end of 2007. Given the institution's internal problems, the government preferred not to renew it, thus interrupting the evaluation of this GMO. In order to deal with the ("urgent") MON810 case, the French State created a provisional committee, the Preparatory Committee of the High Authority on GMOs (CPHA in French), which issued an opinion, serving as the basis for the French safeguard clause (moratorium) on this maize. Time passed and the law on GMOs created a permanent GMO evaluation committee (or provisionally permanent), the High Council of Biotechnologies, made up of a Scientific Committee (CS) and an Economic, Ethical and Social Committee (CEES), which once again, given the "urgency", was immediately referred the dossier for renewing authorisation of MON810. It issued its opinion on the 22nd of December 2009 (1). These lines are being written in September 2012 and MON810 has now been authorised for four years due to an extension of its authorisation, which should normally have expired. For the European Commission this is a very good way of serving the interests of Monsanto without having to face the arguments made by many Member States who have banned this GMO in their country. Having said that, this period of time was put to good use in consolidating the cases made by small-scale farmers' associations and trade unions involved in the fight against GMOs, meaning that the authorisation dossier for MON810 was subject to independent expertise.

Greenpeace and Friends of the Earth Europe in particular, published soundly argued criticism of EFSA's opinion (2), whereas GIET, supported by France Nature Environnement and Inf'OGM, proved that EFSA's opinion was at fault because it clearly was not of a scientific nature. As these arguments were taken into consideration by political bodies, the affair was taken to a European level.

The Preparatory Committee of a High Authority on GMOs (CPHA in French) marked a turning point in the history of GMO evaluation. Whilst Marc Fellous, chairman of the previous Commission, the CGB, had campaigned and still does in favour of authorising the cultivation of MON810 in France, and who is the current founding chair of the AFBV (3), an association dedicated to promoting GMOs, Senator Le Grand, the chair of the CPHA who is particularly open-minded, ensured that all arguments, even those unfavourable to MON810, were heard. As a result, he became the target of a large number of attacks and was even hated by some of his colleagues. Senator Jean Bizet (also from the UMP) declared, in his statement: *"We executed him at 2.18 in the morning. He died on his feet, but was still twitching"* (4).

1, http://www.hautconseildesbiotechnologies.fr/spip.php?rubrique1
2, Greenpeace & Friend of the Earth-Europe (2009) « A critique of the European Food Safety Authority's opinion on genetically modified maize MON810 ». Greepeace Technical Note Number GRL TN 06/2009, http://www.greenpeace.org/espana/Global/espana/report/other/una-cr-tica-al-dictamen-de-la.pdf
3, Association Française des Biotechnologies Végétales (French Association of Vegetable Biotechnologies)
4, http://www.lexpress.fr/actualité/environnement/ogm-le-coup-de-colere-du-senateur-le-grand_471982.html and for the original video broadcast on Public Sénat: www.publicsenat.fr.cms.emission/emission.html?idE=56979

Following requests made by FNE, the French government opened up the PCHA panel of experts to a statistician. His report was particularly important and the opinion given by the PCHA included this sentence: *"a large majority of participants have stressed the shortfalls of 90-day tests, which have insufficient power. In fact, the methodology used on rats (validated by the OECD) does not allow conclusions to be drawn on whether or not there are significant differences between the test and control groups"* (5). Plainly speaking, this means that if the protocol allows us to say that MON810 does not kill rats immediately, it does not permit to reveal another possibly existing pathogenic effect, even if considerable.

Armed with this expertise which is hard to contest (6), the GIET wrote to Mr Barroso, President of the European Commission, (7) on the 3rd of June 2008, to ask if it was possible to rule out the toxicity of MON810, taking the statistical risk into account (GIET does not ask for the impossible), that is to say, by using the following null hypothesis as a bases: *"the groups of rats which consumed MON810 and the groups of rats which consumed conventional maize are different in terms of the parameters studied by Monsanto"*. Nothing more than this. Four years later, the GIET is still waiting for a reply! Apparently the European Union is a democracy.

Even if the respect for citizens alone should have resulted in Mr Barroso's services answering an important question, it is true that nothing in the texts obliges the European Commission to answer an association. Thus the affair could have remained there if two Members of the European Parliament, Luca Romagnoli, from the Italian right and Monica Frassoni, from the European Greens, had not used GIET's open letter as a basis for asking two questions sent to the Commission (8). In addition, Ms Frassoni asked another question, of some interest: "Does the Commission agree that the authorization of a product can only be justified if toxicity tests on it enable toxicity to be excluded? This is a clear question, which requires a yes or no answer.

Just as clear is the main question asked by Monica Frassoni: *"Can the Commission certify that transgenic maize MON810 is non-toxic, within the boundaries of normal statistical risk. In other words: by taking as a basis the null hypothesis H0(zero): "the control group and the test group are different", can potential toxicity be excluded and with what risks for each of the parameters considered? If so, can the Commission forward the calculations in support of that exclusion?".*
Although the Commission is not legally bound to answer questions tabled by an association, it must answer a written question tabled by a European Member of Parliament. Were this not the case, we would fail to see the point of the procedure of written questions and we would also fail to see how this was compatible with a democratic regime. However, as nothing came of it, it was the French government's turn to become involved in the affair and on June the 22nd 2009 (in other words one year later), Mr Jean-Louis Borloo, the Minister of State, Minister of the Environment and the Secretary of State for Ecology, Ms Chantal Jouanno, wrote to Mrs Androulla Vassiliou, European Commissioner for Health, responsible for the MON810 file. In this letter the Ministers repeat Ms Frassoni's question, emphasizing its importance, and conclude: the data available to EFSA should allow the verification requested to be carried out speedily. In order to continue the procedures started with the aim of improving GMO evaluation and to respond to the concerns of Member States on this matter, we believe that the Commission should give a precise answer to the question asked by Ms Frassoni as soon as possible".

In fact, the European Commission did not take long to reply. In answer to the first question asked by Ms Frassoni, it said: *"The Commission admits to the Honourable Member that, in accordance with the requirements of Regulation (CE) n°1829/2003, genetically modified foodstuffs and animal feed must not have negative effects for human health, animal health and the environment, and they can only be authorised if this is the case"*. For the second question, the Commission states that it referred to EFSA's GMO Panel and attached it report. After having reiterated that EFSA was independent, the Commission concluded: *"as a result,*

5, The representative of FNE had already raised the question on statistical power with regard to the opinion given on MON863 with the CGB, however, it had not received any reply.
6, The expert in question, Marc Lavielle, professor at the Paris Descartes University and current member of the HCB, has reiterated his criticism since.
7, See the letter in annex 2, p.46
8, See the questions in annexes 3 (p.48) and 4 (p.49)

EFSA's response, conveyed by the Commission, states that it is the Authority's sole responsibility". A wise precaution taken by the Commission, which explicitly washes its hands of the non-response given by the "Authority" (EFSA). In fact, after having repeated its latest opinion on MON810, concluding it was *"just as safe and nutritious as its non-genetically modified counterpart"*, EFSA stated that the appropriate statistical method consisted of working with the null hypothesis, which assumes that test and control groups are equal. With regard to the question asked, EFSA completely ignored it and none of the figures requested were provided.

EFSA's non-response deserves to be more extensively commented on. Further on we will see how EFSA gave an ad hoc reply, with regard to the choice of the null hypothesis, which was contradicted by EFSA's own recommendations and analyses! In addition, whereas the question asked by Ms Frassoni could not have been any clearer *"Can the Commission guarantee, [..] within the boundaries of normal statistical risk"*, to which EFSA replied that there was always a risk of error (which is also what Ms Frassoni and Mr Romangnoli say, explicitly accepting this error. However, the unavoidable existence of an uncertainty is contrary to the claim made by EFSA in its opinion) and criticizes the MEPs for contesting the 5% risk, which they simply **NEVER DID** (9). This is a very typical example of stonewalling (we put words in the mouths of our interlocutors and then reply that they are wrong (10)) and by this we understand that the European Commission did not want to shoulder responsibility for this "answer".

In order for everything to be clear, and although it is obvious that EFSA side stepped the question, the French government provided these elements to the HCB when it was referred to for MON810. The answer given by the Scientific Committee of the HCB is clear: This is not an answer to the question asked. The exact quotation goes even further, highlighting the incoherence of EFSA's remarks:

"The statistical question was formally asked by Ms Monica Frassoni, Member of the European Parliament (European Commission, May 6th 2009): Can the Commission guarantee that transgenic maize MON810 is not toxic, within the boundaries of standard statistical risk, in other words by using the null hypothesis H0: "the control group and test group are different", can we reject this and at what risk, for each other the parameters considered? If so: can the Commission provide calculations proving this claim?" EFSA did not provide an answer to these issues. With regards to the toxicity studies, EFSA refers to the Hammond and co. article (2006). This study does not demonstrate the existence of an effect of concern for health, nor does it demonstrate rigorously (in terms of

9, See Annexes 3 and 4, p.48 and p.49 for the original texts of the Parliamentary questions and annex 5, p.50 for EFSA's pseudo-response.
10, Moreover, the choice of a 5% risk is not at all compulsory, another risk can be chosen, for example 1% or 10%, depending on what we want to do.

An expert committee which is clearly neutral: the CGB

Created in 1986, the CGB was the first GMO evaluation body in France. For a reminder and analysis of its history, please refer to the work of Christophe Bonneuil and Pierre-Benoît Joly (1). Under the presidency of Axel Kahn, who was passionate about technology and very much a technocrat (He resigned in 1997 because Alain Juppé, the Prime Minister at the time, had not followed the CGB's advice, thus showing that in his opinion, the expert also had to be the decision-maker), the CGB had some reservations about the introduction of genes tolerant to herbicides or resistant to antibiotics, as well as about some trials. However, under the next presidency, that of Marc Fellous, the CGB simply became a chamber of validation.It is highly significant to notice that since the dissolution of the CGB, Marc Fellous and several members of this "neutral" institution have signed a petition in favour of cultivating MON810 and created the AFBV (which, as we saw, Mr Fellous is the chairman of), sponsored by the famous Claude Allègre, and whose founding members include the chairperson of SOFIPROTEOL and current chairperson of FNSEA(2), members of Limagrain, Maiz'Europe, Aventis Crop Science, etc., Almost all the same former members of the CGB (as well as its toxicology expert) belong to another association, AFIS, close to rationalist movements, whose hobby-horse is also the defence of GMOs and denigrating organic agriculture.

1.Bonneuil, C. and Joly. P.B. (2007) *« Plantes transgéniques, expertise et action publique : évolution de la place et du rôle de la CGB de 1986 à 2006 »* (Transgenic plants, expertise and public action: how the place and role of the CGB has evolved between 1986 and 2006), in CGB, 20 years of expertise MAP-MEDD Paris p.20-29
2.National Federation of Agricultural Workers' Union.

inferential statistics) the absence of such an EFSA explains how comparison tests are carried out, in other words, by keeping the following as the null hypothesis, HO: "the control group and test group are identical".
It must be emphasised that EFSA's new recommendations, for the statistical procedures which must be carried out when assessing risks linked to GMOs, take most of the comments below into account: in particular the need to carry out strong analyses and to use equivalence tests. Thus, the European Agency implicitly recognises that the previous procedures are unsatisfactory and that the CPHA's reservations were valid" (11).

Therefore, it is interesting that: not only does EFSA deliberately not address the questions asked by the Members of the European Parliament, but it also contradicts itself and all of this is substantiated by a national expert committee on GMOs. We will come back to this. The recommendation made by the Economic, Ethical and Social Committee (CEES in French) of the same HCB is not without interest as well. In response to the opinion of the Scientific Committee (CS), it reads (12):
"The opinion given by the CS highlights the existing criticisms regarding statistical analysis procedures aimed at evaluating the toxicity of MON810.
Taking this remark into consideration, the CEES insists on the need to resolve this significant methodical problem. In order to justify GMO authorisation, toxicity tests must allow the hypothesis on the product's toxicity to be rejected. However, with regard to the sub-chronic toxicity studies (studies called "rat 90-day"), there seems to be a kind of consensus concerning the insufficient statistical power of the studies presented by Monsanto. As they are presented, comparisons between rats which have consumed MON810 and rats which have consumed a control maize variety, do not provide enough information to be admissible.
The CPHA had pointed this out. The matter was referred to the European Commission in June 2008 by an association (13). In May 2009, Ms M. Frassoni, Member of the European Parliament, asked a written question about this issue (see the question in the opinion given by the Scientific Committee). A similar question was asked in June 2009 by Mr J.-P. Borloo and Ms C. Jouanno. DG SANCO (14) considered it as relevant and referred the issue to the European Food Safety Authority (EFSA). The late answer which was finally given by ESFA does not answer the question asked, as is pointed out in the opinion given by the HCB's Scientific Committee.
As EFSA had protocols and the tests provided by the applicant, as well as the necessary time to analyse them, the CEES wonders about the reasons why it did not answer the question of whether or not these tests could be used scientifically as a basis for its favourable opinion, with regard to the renewal of MON810.
Under these conditions, and without prejudging the toxicity of MON810, the CEES does not understand how it is possible to conclude scientifically, as EFSA's opinion does, that MON810 is as safe, in terms of toxicity, as conventional maize".

On the 13th of January 2011, a Member of the European Parliament José Bové, taking into consideration that neither Ms Frassoni nor Mr Romagnoli were Members of the new European Parliament, asked the same questions again, supplemented with a more detailed introduction (15). He received an evasive answer by the Commission, attached with the same "answer" EFSA had given previously. If at a European level there is a problem with GMO evaluation, there is also a problem with democracy!

In the meantime, as all of this was starting to cause a stir and the French State wanted a real answer to these questions, a study was launched by ANSES which is worth spending time on.

To precisely know the exact statistical power of the tests presented by Monsanto for MON810, we needed to have the raw data. We know that applicants do not provide these data, which nonetheless would allow evaluation bodies to check the interpretations provided by the companies. This is an important issue which

11, http://www.hautconseildesbiotechnologies.fr/IMG/pdf/091222_Mais_MON810_Avis_CS_HCB.pdf
12, http://www.hautconseildesbiotechnologies.fr/IMG/pdf/091222_Mais_MON810_Recommandation_CEES_HCB.pdf
13,This is the GIET's letter to Mr Barroso (Editor's Note)
14, Directorate General for Health and Consumers, in charge of these cases in the European Commission
15, http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+WQ+P-2010-011246+0+DOC+XML+V0//EN

NGOs are pressing in particular. ANSES obtained the raw data in printed form, therefore, unusable for making the calculations directly. The data had to be sent again in electronic form, which had to be checked, all of which took up time and therefore incurred considerable costs. Curiously enough, EFSA's director, Ms Geslain-Lanéelle, when asked about this issue, replied: *"When we met, you asked me about access to raw data in the context of the work carried out by EFSA for risk assessment. When these data are necessary, we request them from the applicant and we then have access to these data in the most appropriate form"*. We do not know why EFSA did not submit these data to ANSES in a usable form. ANSES' report was finally published and it is very educational, even if the conclusions on MON810 are questionable, as we will see.

4.1. The ANSES report on the statistics

The aim of this work was to specify which statistical studies should have been used and under which conditions, to review what had been published on the toxicity evaluation of GMPs, then to apply these methods to the case of MON810. In particular it gives details on the issues of statistical power and the choice of the null hypothesis.

Included in the report, the conclusion drawn from the 17 publications on the toxicity evaluation of the GMP studied is clear: *"The strength of these tests is not calculated and the equivalence test is never carried out"*. In other words there is not much in these publications which can really be interpreted.

The report underlines the importance of sub-chronic toxicity analysis (called "90-day rat") (16): *"This trial appears as a relevant sentinel study to detect the non-intentional effects which were not proven by the other analysis results presented in the file ([for example] molecular or the comparative analysis of the chemical composition)"*. ANSES therefore states that we cannot make do with a comparison of the chemical composition of the plants studied, which contradicts EFSA's readiness to make do with these comparisons ("substantial or compositional equivalence") if no biologically relevant difference appears.

At the same time, ANSES also suggested that it would be necessary, for herbicide-tolerant GMPs (17), to have a group of rats fed with GMPs treated with herbicide. However, despite the repeated requests made my NGOs, this is practically never done and generally speaking, we do not even know whether the GMP tested has been treated or not!

What is most interesting about the case presented is that ANSES developed answers which corresponded to the questions asked by the MEPs and to the "arguments" presented by EFSA by way of reply.

First of all, Luca Romagnoli highlighted that there was insufficient power to the statistical tests used. ANSES' report did what EFSA was asked to do and calculated the power of each test. We understand that EFSA did not want to provide them. ANSES' calculations on the data provided by Monsanto in the MON810 dossier show that: *"one hundred and sixteen tests concerning the variables do not present any significant difference. Out of these 116 tests, 110 present a lack of power comparative to the size of one of the reference effects"*. The same report also highlights that: *"When there is not enough power, difference tests can lead to drawing the wrong conclusion being drawn to an absence of the effect of the treatment"*. **However, it is based on these tests of insufficient power that Monsanto and EFSA affirmatively concluded that the treatment by MON810 had no effect.**

Also with regard to the tests' power, the report adds: *"A theoretical calculation of power, carried out on the basis of the data from the MON810 study concluded that there was sufficient power for all the parameters, if the measurements are taken from 20 animals instead of the 10 which were taken into consideration in the study. In the experiment's protocol for the MON810 study, taking 20 animals into consideration makes even*

16, This is in accordance with a previous report by AFSSA "Opinion of toxicity studies carried out in the context of applications for putting GMOs on the market", February 29th 2008.
17, The work done by ANSES applies generally and does not only concern MON810, which is not tolerant to herbicides.

more sense because this is the number used for each of the groups" (18). Monsanto carried out the experiment on 20 rats per group, but only provided the results for 10 rats! The reasons behind this decision and the method for choosing these rats out of all those in the experiment are, to our knowledge, not commented on anywhere, except perhaps, in Monsanto's publication which describes the experiment in detail (19). However, this publication has been… classified as confidential!

We remember EFSA's argument in the pseudo-answer it gave to the MEPs. EFSA feigned it believed that the 5% error rate (or of 95% confidence) adopted by statistical toxicology tests in the MON810 file was what the MEPS were criticizing (which it was not). Let us recall the precise terms: *"Statisticians would agree that in the statistical analysis carried out there is a small probability (smaller than 0,05) that there could be a difference between the GMO and the control. EFSA is also aware that this probability cannot be eliminated and it will always exist since any statistical test is built on a given confidence level, normally 95%. By accepting such confidence level, EFSA is using an approach accepted worldwide, which constitutes the foundation of any statistical test"*.

So now our Members of Parliament are being accused of attacking the worldwide acknowledged basis of statistics. What audacious, ignorant people! Interestingly, ANSES' expert statisticians also committed this crime against the scientific world by writing: *"The choice of a 5% risk (20) is often arbitrary. Increasing this risk, for example to 10%, would increase the power of the tests (see paragraph on power). This would increase the chances of detecting differences between animals which received a diet containing the GM plant and those which received the control, quasi-isogenic plant. In other words, this would increase the sensitivity of the experiment to be able to detect signs of potential toxicity of the diet studied*".

The problem is that we can read what is written by EFSA itself in its opinion on the way in which "90-day" toxicology tests should be carried out: *"The power of the experiment can also be increased by using a higher significance level than 5 % which is the statistical level most commonly used in biological research"*. And the august committee of experts suggests using a limit of…10% (21). The contradictions in terms are normally not accepted in science, not even sound science.

The principle of toxicology tests is to do everything possible to demonstrate potential differences, which are then analysed by experts (we will come back to this issue). Therefore, it is logical to use, for difference tests, a high statistical risk and in this case 10% is appropriate. EFSA's strategy in its "answer" was therefore to cloud the issue, by focusing on unrelated (and false) topics, aimed at discrediting Members of Parliament and Ministers. Clearly EFSA does not behave like a group of experts whose job it is to enlighten political decision-makers and the population. But it does have something to defend, even if it uses arguments which it knows are fallacious. Because we can be sure this is not a question of incompetence, as we will show later on.

4.2. The dose/response argument

One argument often used by toxicologists is based on the need to have a dose/response or dose/effect relationship (in other words, acknowledging that, in this case, the greater the dose of GMO ingested the more pronounced significant differences will be). In ANSES' report, this argument is used, although in a moderate manner. This is rare. Thus, for example, the minutes of the CGB's meeting regarding MON863, state, without any nuances that: *"significant differences are only relevant if there is a dose effect or a time effect"* (22).

18, Underlined by us.
19, Lemen, J.K., Dudek, B.R. (2001), 13-week feeding study in rats with grain from YieldGard (MON810) corn grain (DK551 Bt) preceded by a 1-week baseline food consumption determination with PMI certified rodent diet #5002, Monsanto Technical Report, MSL 17596
20, A confidence level of 95% or an error rate of 5% are equivalent expressions.
21, EFSA Scientific Committee, Draft for public consultation (2011) *EFSA guidance on repeated-dose 90-day oral toxicity study on whole food/feed for rodents*, p.17, http://efsa.europa.eu/en/consultationsclosed/call/110707.pdf
22, Biomolecular Engineering Commission- Summary report of the session on May 29th 2007, http://agriculture.gouv.fr/IMG/pdf/1-2_cle82c4c7-20.pdf

Thus, if a rat presents an anomaly with a weak dose of GMO but not with a strong dose, the data is considered not to be biologically relevant and is eliminated (23).

However, there are an increasing number of examples for which the old dogma *"the dose makes the poison"* is not valid, in particular in the fields of immunology, endocrinology or oncology. Moreover, and if there is no other argument, this would at least be a question of erroneous reasoning.

In fact, toxicologists use "outbred" rats, in other words those having a certain genetic diversity, in order to increase their chances of noticing resulting pathologies linked to the individual sensitivities. What must be understood is that the two doses of GMO administered (11 and 33%), are given to different animals. One group receives 11% and the other 33%. It is therefore not the same animal which presents a pathology with a weak does and which does not present it with a strong dose.

Let us imagine that only 10% of the French population ate a given GMO, which caused an illness in only 1% of cases. That would account for 65 000 sick people, which is a considerable number. Let us transpose this onto our animals in the experiment. In this case, all the "trial" animals eat the GMO, with one dose or the other. If we have 100 "trial" rats, there is a probability that ONE is sick. Only one, of one gender and for one particular dose. If there are no sick rats with a stronger dose, this does not mean that the GMO is harmless, even if we use the old dogma, according to which effects increase when the dose is increased.

Therefore, there is a contradiction to using rats with genetic variability, aimed at increasing the chances of blurring individual sensitivities and requiring a dose/response relationship in all cases. This means denying the existence of these individual sensitivities.

Let us now refer to this with regard to the "answer" given by EFSA to the Members of the European Parliament and to the French Minister of Ecology: *"As described in detail in the scientific opinion (EFSA, 2009), during the evaluation of MON810 risk assessment the GMO panel did not observe any biologically relevant difference between treatment groups in the 90 days rat feeding study. The only statistically significant differences observed in the rats haematology determinations were present only in female rats at low doses and, importantly for the panel conclusion, these were not observed at high dose levels. Furthermore, these differences were all within literature reference and historical control ranges. For these reasons the GMO Panel consider them to be spurious and of no biological relevance"*.
Once again, perhaps considering that politicians are incompetent in the field of expertise, EFSA uses an argument, in a peremptory manner, which it knows perfectly well to be false. We will come back to this point but we need first to finish with the very interesting ANSES report.

4.3. The ANSES report's conclusion on MON810

After theoretical considerations aimed at improving the use of statistical tools by the applicants, ANSES analyses the MON810 dossier. As we saw, the way in which it was submitted by Monsanto was harshly criticized. Statistical powers were calculated and their weaknesses demonstrated (24), abusive claims concerning the equivalence of the trial and

23, Interestingly, this sometimes also occurs when an anomaly is only observed in one gender.
24, See p.42: *"These results show that, in most cases, experimental data does not allow the following hypothesis to be rejected "the difference between a GMO and the control is greater than the tolerance limit".* This means that if MON810 has some effect on health, the test cannot detect it....

According to EFSA

"A common approach to deal with Type II error [Editor's note: lack of power] in proof of difference test, but one of dubious validity, is the calculation of statistical power from the experimental data obtained (so-called retrospective or post-hoc power analysis). In this approach an applicant may seek to compensate for a possible lack of power in a relatively poorly replicated experiment by adjusting the size of the experiment (the Type I error rate), which uniquely determines the retrospective power of the experiment". However, this is exactly what ANSES did with MON810…

EFSA (June 2008) "Statistical considerations for the safety evaluation of GMOs. Draft report on general guidance"

control groups are dismissed, thus implying that EFSA should never have validated such a dossier, especially under the terms used to do so. Unfortunately, ANSES does not stop there and tries to redeem MON810 nonetheless, as if there were an apparent need to validate this GMO at all costs.

In order to do this, after writing a 28-page document denouncing the statistical errors made, ANSES took the same data provided by Monsanto, based on a protocol which had been considered defective, and proceeded to carry out a series of mathematical corrections to make the unusable useable.

The calculation of power must be done BEFORE the protocol is created, according to the size of the minimum effect which must be discerned, and to the variance, possibly estimated using data from existing scientific databases (25). We cannot conclude anything from data with insufficient power because of how the protocol was created (see inset on page 23). Let us allow…EFSA (26) to say a few words: *"No amount of statistical significance can rescue a badly designed study"*. It is remarkable that, when one of these organisations outlines the rules to be followed, they do so with the rigor and knowledge expected. However, they forget their own prescriptions as soon as it is a question of applying them to a case of particular commercial importance (27).

In view of this, based on the 33 statistical differences found after the corrections, a toxicologist was called upon to decide whether or not they were biologically significant and he eliminated them, one after the other (but without going into the details of his argument), essentially using as a basis the lack of a dose/effect relationship, the lack of convergence as well as histological data, of which the importance is highlighted everywhere.

4.3.1. Histological data

At the end of the experiment, autopsies are performed on the rats. An anatamopathological and histopathological test is carried out: the different

25, It must be noted that those recommended by EFSA happened to be those of ILSI!.
26, Scientific Opinion. Statistical Significance and Biological Relevance. *EFSA Journal* 2011; 9(9):2372
27, There are many other publications which denounce this methodological error, for example Wlater, S.J. "Consultats'forum: should post hoc sample size calculations be done?" *Pharamceut. Statist.* 2009; 8.163-169 or the very explicit editorial: Andow, D.A. "Negative and positive data, statistical power and confidence intervals". *Envir. Biosafety Res*. 2 (2003) 75-80

The "concept" of substantial equivalence

Most scientific work consists of comparisons. Given that access to what is absolute is not appropriate, the relative properties are studied by comparing them to one or more controls, judged to be well enough known for the question asked. In the case of genetically modified crops, the evaluation is carried out in relation to normal plants of the same species (potatoes, maize, tomatoes, etc.) The idea behind this comparative approach is that if we do not find any difference between the GMP and its non-GM counterpart (having really looked for it!), used for a long time and without any known disadvantages, there is a probability that the GMP would not cause any problems either. That is why, in principle, comparators must include varieties actually consumed and not just the variety from the collection which was used for transformation.
None of this can be contested in principle. However, in practice, as not everything can be studied, one would have to know what needs to measured beforehand. What are the parameters relevant to the case, which are not yet known and where a problem might arise? That is why it is necessary, in all cases, to carry out more global tests, such as toxicology tests.
The principle of substantial equivalence, sometimes presented by some pro-GMO activists as a global comparative approach, is actually based on an absurd assumption: the comparison of constituent elements (amino acids, fatty acids, minerals, etc.) and some other descriptors, include all the necessary information for stating the difference or equivalence between a GM food or made from GMOs and its normal comparator. When we know that with the same amino acids we can make a large number of different proteins and that one protein can have the same sequence of amino acids but different spatial conformations, the question of the scientific validity of such a procedure is over and done. You can find in the previously quoted work *"GMO myths and truths"* a documented analysis of the issue, whichis not useful to repeat here. (1)

1. Antoniou M. et al *GMO myths and truths – an evidence-based examination of the claims made for the safety and efficacy of genetically modified* crops, June 2012 Earth Open Source, p.24

organs are examined, to look for possible lesions, then they are cut into very fine slivers which are placed and mounted onto glass slides, These are then dipped into different stains and: according to how these stains fix onto constituents, microscopic examination of tissues and cells morphology is possible. This stage is clearly very important in toxicology, given that it shows possible tissue or cell lesions. According to them, it is on these tests that the majority of toxicologists' decisions are based.

Having noticed that none of the members of the ANSES panel behind the report had any declared competence in histopathology, Inf'OGM asked the institution who had read the slides. The Director General answered without stonewalling:
"The histological slides from the study analyses in the ANSES report were not examined by the experts of the CES" (28).

As a result, the same question was put to ESFA and the answer was the same (29). In fact, other than the laboratory which had carried out the analysis for Monsanto, no national or European expert examined the histology slides despite experts themselves speaking of this analysis as crucial. This denotes their trusting nature.

4.4. The strange position of EFSA

Particularly after reading the pseudo-answer given to the Members of Parliament and the French Minister, we might conclude that EFSA's GMO Panel is incompetent. A quick look at the experts' CVs and publications would be enough to refute this impression. Most importantly, one only has to read EFSA's recommendations on the statistical methods to be used to see that they are absolutely contradictory to the practices of the applicants (in general, and not just in the MON810 case taken as an example). During a meeting with stakeholders in Berlin, in June 2009, the GMO Panel presented its draft guidance on environmental risk assessment, which specified: *"For each study and each parameter, an analysis of the statistical power must be provided, for each difference test and equivalence test, based on a power of 80% for the expected tolerance limit, and assuming a 5% type error rate*.

Or for instance: *"The Scientific Committee recommends that the nature and magnitude of changes or differences observed in the studies, which would be considered relevant, must be established before the studies begin (30). The size of the effects must be used to design studies with sufficient statistical power to be able to detect effects when there are real differences of a certain size"* (31). In another document (32), EFSA's GMO Panel states that two tests, difference and equivalence, must be carried out, specifying that the difference test alone *"may not be relevant from the viewpoint of food safety"*. In the same opinion, EFSA warns against using data taken from outside the experiment itself, as is the case with the reported and published data used by the applicants and toxicologists. This is in order to ensure that the data on non-GM commercial varieties are *"obtained in identical conditions to that of the GM and its conventional counterpart. This has the major advantage of eliminating uncontrollable confounding effects"* (33). Then the point is further hammered home, in connection with the method for establishing the tolerance limit, where it is clearly stated: *"Therefore limits obtained from literature data can be expected to be wider than limits obtained from concurrent data"* (34).

We could quote other excerpts from other works by EFSA, which are all in the same vein: this institution is evidently perfectly aware of the current state of affairs in science in these areas and knows the methodologi-

28, CES: Name for the group of experts created by ANSES to work on the report in question. Letter from the director of ANSES to the chairman of d'Inf'OGM, Sepember 8th 2011.
29, Letter to the director of EFSA to the chairman of d'Inf'OGM from April 26th 2012.
30, Underlined by us.
31, EFSA Scientific Commitee. Scientific opinion. « Statistical Significance and Biological Relevance ». *EFSA Journal* 2011 ;9(9):2372
32, "Scientific Opinion on statistical consideration for the safety evaluation of GMOs". EFSA Panel on genetically modified organisms (GMO) *European Journal* 201 0;8(1):1 250
33, *Idem*. p.23
34, *Idem*. p.25

cal rules. It is therefore in completely bad faith that it uses its authority to avoid the extremely bothersome questions made by associations, Members of Parliament and Ministers. As for the European Commission, it is clearly no fool given that it insisted on the fact that as EFSA was independent, it was responsible for the "answer" given, which was a good way of passing the buck. Nonetheless, in practice it is the European Commission which makes the decisions authorising GMOs or not, based on the opinions given by EFSA. Therefore, the Commission cannot merely transmit these views in an irresponsible manner, or, so that things are clear, EFSA should be the decision-maker, which we do not want.

Now the question still remains as to why EFSA adopted such an attitude. The pseudo-answer given to the Members of Parliament is not an isolated case. The history of the revision of the Guidelines speaks for itself: taking advantage of the fact that it held the Presidency of the European Union, France asked the question about evaluation during the Council of Ministers of the Environment. On the basis of the dossier, a unanimous decision was taken in December 2009, requiring the European Commission to improve assessment. The Commission therefore gave EFSA a mandate to prepare new assessment guidelines, aimed at giving guidance to applicants for preparing their dossiers. EFSA got down to work and put forward a first draft of these recommendations, which included practically everything that we had asked for, in particular, the correction of statistical tests, in accordance with everything we have said in the present work. Only the comparisons with reported and published data were not included, as they had not been (and have still not been) denounced (35). A presentation of the draft guidelines was given, in the presence of some associations and on that occasion, the FNE representative realised that right in the middle of the document containing substantial improvements, there was a sentence which said, in substance, that if the comparison of the GM plant's constituents with the conventional non-GM control did not reveal any relevant biological difference, then **NO toxicological or environmental evaluation had to be carried out**. This is what EFSA called an improvement to evaluation. Given that compositional differences which are revealed in the dossiers are still considered not to be biologically relevant, using the ad hoc arguments which we have denounced extensively here, this is equivalent to not evaluating any GMO and falling into line with the United States, where only "substantial equivalence" is required in order to be given the go ahead by the Administration.

It is impossible to think that the experts of official assessment agencies can sincerely claim that the results of analyses carried out on a certain number of basic constituents mean one can deduce their global properties. However, this is what we find in the OECD report on the subject (36): *"The main conclusion of the report is as follows: if a new food or food component is found to be substantially equivalent to an existing food or food component, it can be treated in the same manner with respect to safety. No additional safety concerns would be expected"*.

EFSA is obviously only one of the bodies which, to paraphrase David Schubert, from the Salk Institute (37) *"rubber-stamp a process designed to increase public confidence in, but not ensure food safety"* (38).

35, Only making comparisons with the data which suit the applicant is clearly one of the most effective ways of eliminating statistically significant differences.
36, OECD (1993) Safety evaluation of foods derived by modern biotechnology. Concepts and principles. http://www.oecd.org/science/biosafety-biotrack/41036698.pdf
37, Independent Institute based in California.
38, Quoted on: http://www.bangmfood.org/quotes/24-quotes/29-regulatory-breakdown

5. Allergological testing

5.1. Basic concepts

One of the functions of the immune system is to fight against foreign pathogenic agents (viruses, bacteria, molecules…). Seen by the immune system, a molecule is an antigen. The immune response is not against the entire molecule, but against fractions called epitopes. Two types of immune responses are possible and are often linked: cellular immune response (carried out by T lymphocytes) and those mediated by antibodies, which are complex glycoproteins produced by B lymphocytes and which can circulate in biological liquids (including blood). Even though this is completely artificial (T lymphocytes help to guide the production of antibodies through B lymphocytes), we will separate the cell responses from the antibody responses, by only focusing on the latter.

After contact between the immune system and a foreign immunogenic agent (for example, a virus), an immune response is developed, which will result in the production of antibodies, whose specificity and affinity with the antigen will increase over time. At first, the immune response is not very effective. However, it puts in place a memory of the antigen which allows antibodies to be produced very efficiently, after the reintroduction of the initial antigen or of a similar antigen (called a “cross-reacting antigen”). There are several categories of antibodies. The most important as a “secondary” response (after reintroduction of the antigen) are called IgG (Immunoglobulins type G). However, sometimes instead of protecting the individual, the immune response can go beyond this aim and cause problems. This happens particularly when in response to an antigen, the immune system develops an allergic reaction mediated by IgE antibodies. The antigen responsible is then called an “allergen” but it is the immune system that decides whether an antigen is an allergen or not.

If the human population (this is true for all vertebrates) comes into contact with an antigen, a certain proportion of individuals might develop an allergy to this antigen. This percentage varies according to the antigen, the population, the environment and the time. Currently, the tendency to respond allergically to an antigen is increasing and constitutes a major public health problem.

An allergic response is not only linked to the characteristics of the antigen but to a complex group of factors, including the antigens’ characteristics (some have a greater tendency than others to cause an allergy), the characteristics of the immune system, those of the individual (in particular their genetic susceptibility) and of society, all of which exist in a given environment (given but indefinable). Therefore, the evaluation can only try to reduce the probability of allergic reactions appearing but cannot in any way predict the individual behaviour of the immune system with regard to any given antigen in a given context at a given time. It is not a question of making a prediction with a known error rate but of trying to stop what we can, which is not the same thing.

Requiring a new food product to present no apparent risk or even a known risk of allergenicity is asking the impossible. This is not a reason in itself to ban the dissemination of this product (1). However, presenting an allergological evaluation as being capable of answering the question about risk is intellectual swindle. As with the rest of the present work, it is not the conclusions of the evaluation studies which interest us but rather the real meaning of this evaluation (without decision-makers having to understand them in order to

1, However, it seems obvious that in case of suspicion, in the very least there should be appropriate labelling for groups of people at risk. The rest depends on a political decision.

make their decisions; decisions which are not based on evaluation data but on a complex assessment, using scientific data and non-scientific factors such as the experts' experience).

Standard toxicology tests, like the sub-chronic 90-day rat tests for example, seen above, even when carried out correctly, are ineffective in this field. However, there are a few basic ways which can avoid some problems, if, once again they are properly carried out, such as synthesizing a known allergen by the crop; and of course these methods must be used. If these tests, which we shall examine, show there is suspicion of the product's allergenicity, this is important positive information. If they find nothing, all this means is that nothing has been found. A few quotations from experts confirm this:
"Currently, these techniques are informative but non-conclusive" (2);
"To this day, we cannot reliably and objectively assess or predict their allergenicity [editor's note: of GMOs]" (3);
"Allergenicity is not an intrinsic, fully predictable property of a given protein but is a biological activity requiring an interaction with the immune system in predisposed individuals. It, therefore, depends upon the genetic diversity and variability in environmental exposures in the individuals" (4).

Eliminating 2% or 90% of the risk is not the same thing. In the case at hand, the tests allow in principle to eliminate a certain percentage of risk, but one does not know what this percentage is. Once again, whilst nobody can be expected to do the impossible, the scope of the expertise used has to be clear. When this uncertainty is interpreted as *"the approach adopted is that of the weight of evidence"*, initially proposed by the Codex Alimentarius and repeated by EFSA, this is a complete contradiction. We could decide to call "granite cobblestones" a slab of butter. The definition of the product and everything linked to it requires clarity for all, and it must be shown that this is of interest. In the case at hand, EFSA's description of "weight of evidence" does of course take into account the limited predictive scope of tests but who amongst decision-makers and commentators are going to read EFSA's 168 technical pages which specify this?

In its opinion of the GM Amflora potato, the CS of the HCB announced:
"Given that potential allergenicity cannot be evaluated from one test alone, the recommended approach is the "weight of evidence" (5) which depends on a range of arguments".

This "weight of evidence" means in fact that nothing concrete supports the conclusion. Sometimes it is good to have an interpreter to read the experts' opinions. Let us look at this range of arguments one by one, which, it is worth noting, were established by ILSI (6), which we will talk about later.

5.2 "The recombinant protein (7) comes from a non-allergenic protein"

It is a matter of common sense that if we know the allergenic nature of a protein, it is better not to deliberately synthesize it through a GMO. However, this is what was done by Pioneer Hi-Bred with an improved soybean, with the introduction through the transgenesis of DNA coding of a strong allergen from the Brazil nut (8). Thus proving that carrying out this kind of verification is not useless.

2, Wal, J.M. During a seminar of toxicology and allergology of the HCB on the 29th of September 2010. Unpublished.
3, Wal, J.M. « Evaluation de l'innocuité des aliments issus d'organismes génétiquement modifiés » *Rev. Fr. Allergol*. (1 997) 37 (3):326-333.
4, EFSA "Scientific opinion on the assessment of allergenicity of GM plants and microorganisms and derived food and feed" *EFSA journal* 201 0:8(7):1 700
5, It seems that in the context of its permanent improvement programme, the HCB's CS has given up on this misleading wording.
6, It seems that in the context of its permanent improvement programme, the HCB's CS has given up on this misleading wording.
7, That is to say the protein "of interest", encoded by the transgene. For example a Bt protein.
8, Nordlee, J.A., Taylor, S.L., Townsend, J.A., Thomas, L.A., Bush ,R.K. "Identification of a Brazil-nut allergen in transgenic soybeans " *N. Engl. J. Med* (1 996) 334:688-692

However, most proteins of interest encoded by current transgenes are often bacterial. Yet these products have hardly been documented. Some Bt proteins have been used in agriculture for a long time through spraying, however, although Monsanto claimed in its renewal application of MON810: *"Bacillus thuringiensis, the source of gene Cry1Ab (9), does not have an allergenic history"*, it all too quickly forgets that the Cry (Bt) protein produced by MON810 is not the one produced by Bacillus thuringiensis and it is not presented in the same context.

In addition to the possible directly allergenic nature of a product, this product happens to act like an adjuvant. In this case, the immune response (which can be allergic) is not aimed at the substance. However, the substance increases the reaction to another component. Thus vaccines contain adjuvants aimed to increase the efficiency of immune response against the targeted antigens. These adjuvants can also guide the immune response towards protection or allergic reaction.

The GMO group of the Norwegian Scientific Committee for Food Safety raised these questions with EFSA, with regard to six Bt GMOs (10), without receiving a clear answer. This Norwegian committee had used publications demonstrating the adjuvant role of certain Cry1Ac-type Bt proteins as a basis and considered that given the similarities between these and structures and actions of Cry (Bt) proteins, they also needed to be studied from this angle. The answers given by EFSA (11) deserve to be studied in detail. We will only quote one significant excerpt: *"the assessment of allergenicity of GM foods/feeds as currently performed according to Codex Alimentarius and EFSA Guidance Document (EFSA, 2006), is essentially focussed on IgE mediated hypersensitivity, and so far the issue of adjuvanticity is not explicitly addressed"*. How reassuring!

5.3. In vitro digestion testing

In order to be allergenic, a substance must be able to come into contact with the immune system's cells. The idea behind this digestion test is that if a substance is quickly and totally broken down during digestion, it does not reach these cells and is not immunogenic. This test was created based on an article by Astwood, Leach and Fuchs from 1996 (12) and all GMO authorisation applications refer to it. However, by focusing on sensitization through digestion, we forget that this can also happen through breathing (GMO dust during harvesting and subsequent handling) as well as through the skin.

At this point, it is appropriate to digress slightly, in order to explain very briefly the history of how GMO assessment was established:
An article in the *New York Times* (13), backed up by accounts of those directly involved in negotiations, informs us about the creation of the assessment rules:
"In late 1986, four executives of the Monsanto Company, the leader in agricultural biotechnology, paid a visit to Vice President George Bush at the White House to make an unusual pitch.
Although the Reagan administration had been championing deregulation across multiple industries, Monsanto had a different idea: the company wanted its new technology, genetically modified food, to be governed by rules issued in Washington — and wanted the White House to champion the idea."

9, Cry1Ab is the name of the source Bt protein used for MON810.
10, Panel on Genetically Modified Organisms of the Norwegian Scientific Committee for Food Safety (28 juin 2006) "Response concerning further justification and clarification on specific comments by EFSA", http://www.vkm.no/dav/4af53b9c47.pdf
11, Bilateral technical meeting between members of the EFSA Panel on genetically modified organisms and the VKM Norwegian delegation (13th of January 2009), http://www.efsa.europa.eu/en/gmomsmeeting/docs/gmo090113no-m.pdf
12, Astwood J.D., Leach J.N., Fuchs R.L. (1 996) « Stability of food allergens to digestion in vitro » *Nature Biotechnology* 14:1 269-73
13, Eichenwald K., Kolata G., Petersen M. « Biotechnology food : from the lab to a debacle » (25th January 2001) *New York Times*, http://www.nytimes.com/2001 /01 /25/business/25FOOD.html?pagewanted=all

As Marie-Monique Robin explains in *"The world according to Monsanto"* (14), this company, which had been badly affected by several scandals, wanted official bodies responsible for assessing GMOs to make them acceptable to the public. Therefore, regulation was needed but not so as to impede Monsanto's projects. Let us go back to the *New York Times* article: *"In this area, the U.S. government agencies have done exactly what big agribusiness has asked them to do and told them to do," said Dr. Henry Miller, a senior research fellow at the Hoover Institution, who was responsible for biotechnology issues at the Food and Drug Administration from 1979 to 1994"*.

As M.M. Robin recalls, this is when the "concept" of substantial equivalence was created, with no scientific basis, but which is used for assessment in the United States and will soon be used in Europe if EFSA has its way. With regard to allergenicity assessment, both the Codex Alimentarius (FAO/WHO), and EFSA use ILSI's recommendations (15) as a basis. They are just as neutral as its members (Monsanto, BASF, Dow Agrobioscience, DuPont, Cargill, Bayer Crop Science, Novartis, etc.), whose role was extensively denounced by the European Member of Parliament José Bové and associations such as Testbiotech (see inset). The close bonds which tie EFSA to ILSI and the industrialists who are members of it are well known and led to the European Parliament not discharging EFSA for its management in 2010. We return to the subject when we see ILSI bases its digestibility test, a pillar of GMO allergenicity "assessment", on the 1996 publication quoted below by…. James D. Astwood, whose biography (16) tells us he *"joined Monsanto Company in 1994 to establish a program in food allergy risk assessment and was promoted in 1997 to Director of the Product Safety Center"*. Both of its co-authors, John N. Leach and Roy L. Fuchs were also employed by Monsanto. As an aside, the biography tells us that James Astwood participates in the activities of the European Academy of Allergology and Clinical Immunology, the American Academy of Allergy, Asthma and Immunology and is reviewer for two scientific journals: *the Journal of Agricultural and Food Chemistry* and *the Journal of Allergy and Clinical Immunology*.

Now what remains to be seen is the validity and scope of this test which consists of incubating the purified protein of interest in a liquid containing pepsin (a proteolytic enzyme produced by the stomach) and enough hydrochloric acid to reach a pH of 1.2. One speaks of a test for digestibility or resistance to pepsin.

14, Robin M.M. *The world according to Monsanto* (2010), eThe New Press – New York.
15, EFSA (2010) "Scientific opinion on the assessment of allergenicity of GM plants and microorganisms and derived food and feed", p. 87
16, http://www.animalbiotechnology.org/symposium/bios.htm

EFSA – ILSI

IIf there is one name which revealed the relations between EFSA and ILSI, it is Diana Banati. Member of EFSA's Management Board between 2006 and 2012, Diana Banati declared she had a small role in ILSI. In September 2010, José Bové revealed that this "minor role" was in fact a position as member of ILSI's director council. This revelation did not prevent Diana Banati from being elected Chair of EFSA's Management Board in October 2010, after having been relieved of her duties at ILSI around the same time. Even if neither the European Commission nor EFSA did anything since then, Ms Banati herself, resigned from EFSA in May 2012 to go back to her post at…ILSI! In a letter to the European Commissioner John Dalli (1) in December 2010, the association Testbiotech, wrote *"Harry Kuiper has been chairman of EFSA's GMO group of experts since 2003. Just before joining EFSA, he was member of a working group created by ILSI […] According to ILSI itself, the working group had an impact on EFSA's guidelines for assessing risks linked to genetically modified plants […] Other problems also arose because ILSI set up a database used by EFSA, to compare the components of genetically modified plants with those of conventional plants"*. To be clear, in order to evaluate the authorisation application cases submitted by companies, EFSA uses an approach promoted by the companies themselves and with tools provided by the companies. Therefore these companies had managed to provide the questions, answers and corrections to an exam!In February 2012, in its report "Indigestible Conflicts", the Corporate Europe Observatory wrote, as a summary of the situation, that EFSA *"gave credibility to ILSI as a "scientific" organisation. In order to do this, EFSA organized events with ILSI, paid experts to attend ILSI's events and was officially represented in ILSI's working groups"*(2).

1, http://www.testbiotech.de/sites/default/files/Letter%20Commission_ 21_12_2010_0.pdf
2, http://www.corporateeurope.org/ sites/default/files/conflits_indigestes_0.pdf

In its scientific opinion on the assessment of allergenicity, EFSA justifies using an in vitro digestion test, such as the one defended by Astwood and his colleagues: *"The justification behind use pepsin-resistance under standardized conditions, as proposed by FAO/WHO and the Codex Alimentarius is that for some food known food allergens there is a correlation, even if there is no direct causal relationship, between their resistance to pepsin and their allergenic properties"*. Jean-Michel Wal, EFSA and WTO expert, expresses himself in these terms (17): *"On the basis that 1) allergenicity is essentially due to the intact protein molecule and 2) the more a protein is resistant to hydrolysis during gastric and intestinal digestion, the greater its chances are of being absorbed intact by the intestinal mucosa, and thus of performing its immunoreactivity at the level of immunocompetent cells; the authors of the American report (18) propose using an in vitro digestion model to measure the resistance to proteolysis"*.

Therefore, there are two presuppositions which support the validity and scope of the test. However, for the first one, J.M. Wal himself (as well as EFSA's opinion) highlights: *"it has now been clearly demonstrated that peptide fragments, even those which are relatively short, retain a non-negligible part of the allergenicity"*. With regard to the first presupposition, the same publication specifies: *"a food protein sensitive to enzymatic attacks and degraded during digestion, such as whole casein, has proved to be an allergen which is just as powerful as beta-lactoglobuline, a globular protein resistant to proteases"*.

Generally speaking, this in vitro digestion test has the vital merit of favouring the needs of GMO producers:
a – It is "in vitro", in other words, in a test tube. However, gastric mucosa, which protects the stomach from its own digestive juices, contains phospholipids (phosphatidylcholines in particular), which protect against pepsin action (19). Moreover, under these conditions the simulated gastric juices are stable, whereas during digestion, its composition evolves considerably;
b – A purified protein is introduced, whereas under physiological conditions, the protein is in a complex and variable food matrix. In particular, there are emulsions which considerably modify the protein degradation process, as well as other factors (20);
c – A protein, as produced by the plant, often undergoes post-translational changes (namely glycosylations) which lead to several isoforms being expressed. Only testing one purified protein (and often it is a recombinant protein generally produced by E.Coli (21) bacterium) does not correspond to reality;
d – Only the protein of interest is tested and not the food as it will be consumed. However, the allergenicity of the whole plant can be affected by inserting one or several transgenes, either because of the insertion itself, or because of the pleiotropic effects (multiple effects linked to one gene);
e – The simulated gastric liquid has a pH of 1.2, in other words it is very acidic, a lot more acidic than real gastric juices are during digestion. Similarly, the pepsin/protein ratio is very high in the test, as it is carried out now. In its previously quoted scientific opinion, EFSA specifies (p.113):
"Such ratios may be considered far in excess of those likely to be found in the stomach[…] approximately 1 unit pepsin is secreted for every 3 mg of protein consumed. This compares with approximately 1 unit pepsin/µg protein used in the pepsin resistance assays".

Under conditions that are so far removed from reality (3000 times the pepsin does in a hyper-acidic environment!), it is clear that the results are of very little interest. In fact, in its file on MON810, Monsanto concludes: *"Therefore, any Cry1Ab protein consumed would be rapidly degraded in the gastric system"*, which

17, Wal J.M. (1 997) Evaluation de l'innocuité des aliments issus d'organismes génétiquement modifiés » (Assessing the safety of foods made from genetically modified organisms) *Rev. Fr. Allergol.* 37 (3) : 326-333
18, In other words ILSI and IFBC (International Food Biotechnology Council), another institute created in 1988 by ILSI and IBA (Industrial Biotechnology Association) and whose members include : Monsanto, DuPont de Nemours, Pioneer, Coca Cola, Nestlé USA, Ajinomoto, Quaker Oats, etc.
19, Moreno F.J., Mackie A.R., Clare Mills E.N. (2005) « Phospholipid interactions protect the milk allergen alpha-lactalbumin from proteolysis during in vitro digestion ». *J. Agric. Food Chem.* 53:981 0-981 6
20, Kaur L., Rutherfurd S.M., Moughan P.J., Drummond L., Boland M.J. (201 0) « Actidin enhances gastric protein digestion as asserted using an in vitro gastric digestion model » *J. Agric. Food Chem*. Apr 28;58(8):5068-73
21, Therefore, we test the effect, structure and functionality of a protein expressed in a plant on a microbe protein.

contradicts Guimaraes and colleagues (22), who demonstrated that the protein Cry1Ab (in particular the Bt protein of MON810) was in fact totally and quickly degraded under the conditions stipulated by Astwood and used by Monsanto, with a pH of 1.2 and a high pepsin/protein ratio, but that it was *"only slightly degraded at pH2 and conserved its immunoreactivity. Furthermore,* ***Cry1Ab proteins were demonstrated to be stable in a more physiologically relevant in vitro digestibility test*** *(pH 2.5, pepsin-to-substrate ratio 1:20 (weight/weight) with phosphatidylcholine."* (23)

Other similar examples exist with the major peanut allergens, which conserve their immunogenicity after degradation under physiological conditions, for example.

Let us quote another sentence from this publication (p.3227):
"Although no clear causal relationship has been clearly established between digestibility and allergenicity, stability to digestion is still considered to be a predictive tool to assess the allergenic potential of a protein".

There are other criticisms of the test, criticisms which are especially expressed very clearly by EFSA's experts. In particular, it is emphasised that in a variable population, as we would expect: there are slow digesters and fast digesters, acidity is affected by the consumption of alcohol, young children do not have a digestive maturity comparable to that of adults, many people take anti-acid medication (24) for stomach ulcers and "heartburn", etc. We could also add, as we are forgetting that the population does not consist solely of young, healthy, well-fed adults, that when a person does not eat every day, the stomach becomes dormant. By way of comparison, if we put vibrio cholera in Astwood's and his collaborators' simulated gastric liquid, it would be almost instantaneously killed and the conclusion would be that it was impossible to catch cholera, a conclusion which we will leave the reader to decide upon, but which, logically speaking, EFSA should validate…

Let us finish this chapter with another quotation yet again by Jean-Michel Wal (25):
"Based on these observations, EFSA's report gives advice, given that it is not in its remit to say that we are abandoning the pepsin test given that it is in the official regulatory texts of the Codex, and it is therefore the Codex which is valid, and EFSA is unable to call into question the regulatory text. Therefore, it is advised that digestion be performed using the protein as it is expressed in the plant and by placing it in its environment if possible, in other words, with a food matrix and not taking a purified protein in an aqueous medium, and that digestion be performed under conditions which are more physiological than is currently the case (26). What has also been advised, is that risk assessment take into consideration people with altered digestion, especially children, whom we know have digestive immaturity, but also people undergoing treatment, the elderly, etc.".

With regard to the Codex Alimentarius, we will quote Inf'OGM (27):
"The norms beyond those of the Codex could be considered as barriers to trade by the WTO. In the event of a dispute, the norms of the Codex represent a ceiling: equivalent or less protection is accepted by the WTO without discussion. Conversely, greater protection must be scientifically justified to convince the WTO of its validity".

22, Guimaraes V., Drumare M.F., Lereclus D., Gohar M., Lamourette P., Nevers M.C., Vaisanen-Tunkerott M.L., Guillon B., Créminon C., Wal J.M., Adel-Patient K. (201 0) "In vitro digestion of Cry1 Ab proteins and analysis of the impact on their immunoreactivity" *J. Agric. Food Chem.* Mar 1 0;58(5):3222-31
23, Underlined by us.
24, Untersmayr E. and Jensen-Jarolim E. (2008) "The role of protein digestibility and antacids on food allergy outcomes". *J Allerg. Cli. Immunol.* 1 21 :1 301 -08
25, Wal, J.M. During an HCB seminar on toxicology and allergology on the 29th of September 2010. Unpublished.
26, The EFSA text says: *"The ability of the pepsin resistance test is to distinguish between allergenic and non-allergenic proteins was initially described by Astwood and co-workers (1996) and whilst not completely confirmed by subsequent studies, it is still considered to have some utility when used in integrative risk assessment."* (p.113). We appreciate the diplomatic tone…
27, Furet, A., Meunier, E., « Le Codex alimentarius et les OGM : une guerre réglementaire sans merci » (GMOs and the Codex alimentarius : a merciless war of regulation), *Inf'OGM* 100

The fear of having to settle a dispute at the WTO is generally dissuasive. Therefore, according to the EFSA expert quoted above, the European Commission has kept the pepsin test, considered to be practically worthless, so that it does not have to be more demanding than the recommendations in the texts of the Codex, which were partly written by ILSI. Did you say “sound science”?...

5.4. Bioinformatic methods

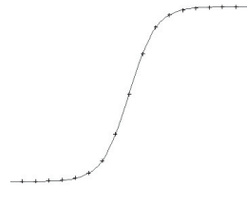
The principle consists in comparing the linear sequences of the protein of interest (the one encoded by the transgene) with known allergen sequences stored in databases. With the help of computer programmes, one investigates whether there is any degree of analogy between the GMO protein’s primary structure and those of the allergens.

A protein is first made up of a chain of amino acids (primary structure) which will then fold into a three-dimensional structure (tertiary and possibly quaternary structure), then modifications can occur (and most often do), in particular the adjunction of sugar residues (or carbohydrates: glycosylation). Further changes are possible. Therefore, although the link between the DNA sequence and the amino acid sequence is strong, it is not absolute.

Computer databases have been created to store the sequences of different recognised allergens. When a new molecule needs to be tested, such as those produced from GMO transgenes, one of the tests consists of comparing its sequence with those registered in these databases.

This has already been highlighted time and again: the allergenicity of a molecule is not a property of the molecule itself and therefore not of its sequence, but rather a result of multiple factors, which are admittedly linked to the molecule but also to the subject and the environment in the broadest sense. Nonetheless, as the molecule does have an influence, it is not surprising to want to predict the existence or not of these factors which facilitate the allergenicity. The objective being to adapt the scope of the conclusions to the real meaning of the data. If a similarity is found between the structure of the molecule studied and the known allergen, we are entitled to request further analysis at least. On the other hand, what is the meaning of a negative result? We will see that it means almost nothing, and knowing that, and as the subject is very complex, we will only be able to touch upon it (but that should be enough).

a - It is the protein's primary structure (the succession of amino acids) that is tested, as it is encoded by the transgene. Once it has been synthesised, the proteins can be modified (and often are), either by the modification of amino acids, or the grafting of sugar residues, or by the adjunction of lipids, etc.
b - During digestion, proteins are in principle denatured, in other words, unwound and cut up by the digestive juices of the stomach and intestine. During this period, fragments can agglomerate or undergo different modifications, which can create new epitopes (the small part of the antigen which attaches itself to the antibodies), unrelated to the initial protein sequence.
c - The databases (several exist, which are not equivalent by the way) are of course not complete. How can one know then what proportion of possible allergens they contain? This would mean that one knows a priori how many there were in total. One can however, have an idea of the proportion by what is recorded in relation to what exists by looking at where we are in terms of the kinetics of completed databases. In fact, after a slow start (the time it took to put the tools in place), the data will increase rapidly, then, because the probability of finding new allergens will fall considerably, the filling-in curve will slow down, all of which will roughly form a sigmoid curve (see inset). When we reach this almost horizontal stage, we can consider that we have almost all the data (in this context and with these techniques). Given that currently the content of these databases is rapidly increasing, we do not know what they contain in relation to the total number of potential allergens. In addition, the content of these databases concern the allergens habitual to the current state of general consumption. One of the essential characteristics of a GMP is that it is a novelty, as it introduces antigens into food (and into the air) which we do not normally come across, at least not in these



forms (28). Therefore, we do not know what the contents of these databases represent in relation to all existing allergens. That is to say that we do not know the impact of a negative conclusion based on examining sequence homologies.
d - An antibody connects to a three-dimensional (or even four, given the bonds which are potentially available) structure in space. This is also true for a denatured polypeptide, which theoretically presents in a linear way. However a non-denatured protein presents itself as a complex fold of this chain of amino acids. This means that the antibody, which is adapting to a surface, will connect to the amino acids which are close to it in space, but which might be very far from the unwound primary chain (this is known as a discontinuous epitope). It is this unwound primary chain (the linear sequence) which is stored in the databases. It is not currently possible to predict discontinuous epitopes based on linear sequences, even if models which try to do so do exist (29,30). AFSSA clearly announced (31): *"The current knowledge about the primary structure (amino acid sequencing) of food allergens does not permit to reveal the common characteristics of allergenicity"*. The proteins which are not or at least not completely degraded in the digestive tract can affect the immune system in their three-dimensional form.
e- Evaluating structural similarities is not easy. Even in the primary structure (the only one which can be assessed in practice), a change in one or several amino acids might not change the protein's immunological properties. On an epitope of around twenty amino acids, only 3 to 5 really count (32). A structural similarity is therefore not merely a question of comparing the position of the amino acids, but rather one which requires algorithms based on hypotheses. Evaluating the homology of an amino acid sequence is not an exact science, even if it has recourse to information technology and mathematicians, which always make it look serious. Different algorithms can be used, which will not produce the same results. It is perfectly possible for an applicant who is not satisfied with the results obtained with one algorithm, to re-do the calculation with another, and only to publish the one which suits him.

In its scientific opinion, EFSA specifies (p.99): *"It should, however, be stressed that all the various computational algorithms available (and reviewed here) are designed to search for (presumed) allergenicity features that are inherent in the protein's sequence/structure, whereas external factors, such as exposure or post-translational modifications (except for search for N-glycosylation sites) are not taken into account. These algorithms are therefore generally well suited for predicting cross-reactivity but currently not for identification of de novo sensitisation potential"*.

f – There are a large number of databases with very unequal content in which even known allergen might not be included: *"β-lactoglobuline [Editor's note: a major allergen], is not reported as an allergen in the databases. It would also not be found as an allergen based on its sequence, according to the suggested homology criteria"* (33). In its report on food allergies, AFFSA warns that: *"The vast majority of allergens present in natural products have not yet been listed, as demonstrated by some two-dimensional immunoblot assays"* (p.22), or even (p.32): *"currently, there is little information available in the databases and too few allergens are listed"*.

Finally, with the knowledge that exists, knowing the theoretical primary sequence of a protein does not allow us to predict its allergenicity. When structural analogies are discovered during GMO evaluation, in spite of

28, And what about putative fusion proteins which are only tested for their toxicity and allergenicity for the databases?
29, Blythe M.J., Flower D.R. (2005) « Benchmarking B cell epitope prediction : underperformance of existing methods » *Protein Sci.* 1 4(1):246-248
30, Ponomarenko J.V., van Regenmortel M.H.V. (2009) « B-cell epitope prediction » in Structural Bioinformatics 2e édition edited by Jenny GU et Philip E. Bourne, p. 849-879.
31, AFSSA (2006) « Allergies alimentaires : les plantes génétiquement modifiées ont-elles un impact ? », (Food allergies: do genetically modified plants have an impact ?)
http://www.ladocumentationfrancaise.fr/var/storage/rapports-publics/074000073/0000.pdf
32, Cunningham B.C., Wells J.A. (1993) « Comparison of a structural and a functional epitope », *J. Mol. Biol.* 234(3):554-563
33, *« les OGM à l'INRA »*, (GMOs in INRA), http://www.inra.fr/internet/Directions/DIC/ACTUALITES/DOSSIERS/OGM/wal.htm

everything, any ad hoc argument will be used to exclude them and not proceed with confirmation serum tests, which are very onerous. As to the negative results which are generally obtained, here again, their impact is not known, but it is probably weak given how little we know about these subjects.

In terms of allergological evaluation, the real meaning of "weight of evidence" can be understood by the yardstick of a quote by an EFSA expert (34):
"As we do not yet know which mechanisms transform an a priori banal glycoprotein into a powerful allergen (35), detailed studies on the impact of modern biotechnologies on the appearance of neo-allergens or the increased creation of new allergenic epitopes should be carried out".

Or from those from the previously quoted AFSSA report (36):
"The methods currently used in assessing the allergenicity of a GMP probably do not take the whole organism into account enough: we evaluate the allergenic potential of a purified protein from microbian origin with the same properties as the protein from the transgene. However, we do not know if other allergens appeared in the protein fraction, or whether allergens which exist in the non-GM control plant in small quantities are overexpressed (37). There are more global approaches, however, with the current state of knowledge, they do not allows us to draw conclusions about the allergenic potential of the organism studied, given the remaining difficulties in interpretation" (p.42).
"All food containing proteins can potentially set off allergic reactions. It cannot be ruled out that the allergenicity of proteins deliberately introduced into a GMP may be demonstrated with the reactions of a certain number of consumers after this GMP has been put on the market. This is particularly true given that currently, the proteins coded by the transferred genes can come from microorganisms whose allergenic potential is not well known, or from organisms which have never been part of the diet of mankind" (p.31).

To be compared to Monsanto's conclusions: *"Taken together, these data lead to the conclusion that the Cry1Ab protein is unlikely to have any allergenic potential and MON810 is as safe as conventional maize regarding the risk of allergenicity"*.

Which is confirmed by EFSA (38): *"Based on these results, the EFSA GMO Panel considers that the newly expressed Cry1Ab protein is not likely to be allergenic"*.

The weight of evidence…

34, Wal J.M. (1 997) « Evaluation de l'innocuité des aliments issus d'organismes génétiquement modifiés » *Rev. fr. Allergol.* 37(3):326-333
35, Aas K. (1 978) « What makes an allergen an allergen » *Allergy* 33:3-14
36, See footnote 31
37, Spök A., Gaugitsch H., Laffer S., Pauli G., Saito H., Sampson H., Sibanda E., Thomas W., van HageM., Valenta R. (2005) " Suggestions for the assessment of the allergenic potential of genetically modified organisms" *Int. Arch. Allergy Immunol.* 137(2):167-180. Epub 2005 Jun 8.
38, EFSA Scientific Opinion Applications (EFSA-GMO-RX-MON810) for renewal of authorisation for the continued marketing of (1) existing food and food ingredients produced from genetically modified insect resistant maize MON810; (2) feed consisting of and/or containing maize MON810, including the use of seed for cultivation; and of (3) food and feed additives, and feed materials produced from maize MON810, all under Regulation (EC) No 1829/2003 from Monsanto », *EFSA Journal* (2009) 1 1 49, 1 -85

6. Other GMO application dossiers for authorisation

The MON810 case is taken as an example, but the others in general are no better. Two dossiers, being reviewed with a view to authorisation in the EU, were the subject of opinions, which were more than harsh, given by the HCB. They concern the Amylopectin-enriched Modena potato (1) and MIR604 maize (2), which produces an insecticide against rootworm.

Apart from a comment made about the Modena case, which clearly highlights how serious the applicant is (in this case Avebe): *"A number of sentences in the dossier are difficult to understand, words are missing, grammatical structures are illogical"*, the HCB also points out the practice (common in GMO cases) of baseless allegations. Thus, the HCB's opinion states: *"it has been demonstrated that plant-sucking insects traveling over a long distance efficiently transport pollen", criticizing the applicant for using an "incorrect" (sic) bibliographical source to state that bumblebees which pollinate potatoes "in general only travel small distances"*. The limits are reached when still on the subject of the pollination of potatoes, the applicant quotes from a scientific article which has encountered the dissemination of pollen over a distance of in fact 1000 metres, and calmly states that it would be very unlikely for pollen contamination to exceed… 20 metres!

Not taking into account embarrassing publications and contradicting the sources quoted by the applicant themselves, one can either envision malpractice or incompetence and it is almost impossible to decide.

Even if the MODENA case wins first prize, the MIR604 case does share the harsh criticisms made by the HCB, which points out that in both cases the statistical studies fail to provide any power calculation (which means they cannot be interpreted), or any equivalence test and that the multiplicity of the tests is not taken into consideration. In other words, the analyses produced appear to be science but are not science, which reminds us of something that was seen earlier.

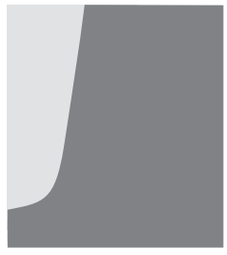
Having no basis for any conclusion (for either of the files), the applicants are nonetheless just as quick to conclude categorically: *"We conclude that compositionally and nutritionally, AV43-6-G7 [Editor's note: reference to the Modena potato] is equivalent to Karnico and other starch potatoe variety" or: "These findings support the conclusion that grain and forage from MIR604 maize are compositionally equivalent to conventional maize varieties except for the presence of the newly introduced intended traits"*.

Logically, the HCB sends the petitioners back to the drawing board, pointing out to them that in no way do the analyses made allow such conclusions to be drawn.

We would like to point out in passing that the arrival of new blood in the club of experts, which until then had been virtually impenetrable, led to noticeable progress in the expert bodies drafting of opinions.

1, http://www.hautconseildesbiotechnologies.fr/IMG/pdf/110412-Pomme-de-terre-Modena-Avis-CS-HCB.pdf
2, http://www.hautconseildesbiotechnologies.fr/IMG/pdf/110413-Mais-MIR604-Avis-CS-HCB.pdf

Conclusion: What is most important is hidden by technical evaluation



Apart from the shortfalls (to put it mildly!) which have been shown, the evaluation of GMOs tends to be passed off as rigorous studies, directly based on data. This is most definitely a parody of science, aimed at political decision-makers and the public. It reaches its peak with the molecular description of transgene insertion. When this is the case, there are sentences such as *"there is only one copy of the transgene, there is no interruption to the gene of the receiving plant…"*. The conclusion: therefore, it is fine. Now that is serious! The pope of all popes, the molecular biologist who can read the world in GATTACA (1), looked and was satisfied. Then the pope of all popes describes maize GA21 (for example). There he says that there are six copies of the transgene, which are more or less complete, that a piece of mitochondrial DNA was carried off by the ball of tungsten which he inserted into the chromosome, and so on… Conclusion: therefore, it is fine.

In fact, as we are incapable of predicting a global effect from one DNA sequence, the pope of all popes validates everything anyway. This is called tautology, not sound science.

Including a molecular description in the presentation of a GMO is nothing more than normal and necessary. Including it in the evaluation when no piece of data can actually affect this evaluation borders on fraud, as it gives weight to considering the GMO favourably without any scientific justification.

Then why does it happen? Why do very competent people, who as we saw, demonstrate in their scientific papers that they are perfectly aware of the limitations of science's predictive capabilities in this area, sophisticated and impressive as that science might be, go off and predict the future using chicken intestines, or almost, while valorizing their real but off-topic scientific capacity in the mind of decision-makers amongst others?

Marie-Monique Robin, Hervé Kempf, José Bové, Testbiotech, we ourselves and many others have uncovered the history of GMO evaluation. Evaluation was decided by agri-business in order to make these techniques, which they had established based on publications written by their own members, more acceptable to the public and is carried out in a context adapted to the needs of these companies, based on files prepared by them, and which cannot be directly controlled, as well as by some experts from their own ranks. In fact, there are independent experts (and we have quoted some (2)), but they work within this system and are themselves those who best represent a way of thinking which leads to the production of GMOs. What is strange to them are not GMOs but naturally, their rejection. In all honesty (and we are convinced that the majority of experts are honest) they identify themselves with these products which are rejected by most citizens (European at least). Because they can find no positive reason for rejection, in this context of expertise designed not find anything, they are even more naturally inclined to follow the general trend. This is because most of them are so convinced of the apparent harmlessness of GMOs, that the main question they really ask themselves is *"but why assess them?"*. This is what agri-business is now supporting, by trying to change the evaluation rules or to get around them.

1, *Welcome to Gattaca* is an American science fiction film made by Andrew Niccol released in 1997.
2, And it is not because an expert has received funding from Nestlé for one a study that he will no longer be independent.

Finally, the criticisms they are subjected to from GMO opponents only cause a reflex reaction to defend their caste, which is even greater when the criticisms come from outside their world and thus appear as a personal attack against them (which to them is of course unjustified).

Many experts who would be willing to admit the limits of their art (especially as the existence of these limits is not at all pejorative) and who would be open to exchanges, dig their heels in when they are criticized. The apparently comfortable separation between experts and civil society is a grave mistake and a hindrance to real democracy and intelligence (3). In particular, it makes the tendency towards clannish opposition worse.

Admittedly, there are also phonies in the industry, amongst the experts (in EFSA in particular), amongst political decision-makers and now even in the civil society associations, but even without them, the system is such that it inevitably keeps the myth alive, which itself further raises his profile, of the omniscient prophet beset by the lack of understanding of ignorant miscreants and obscurantists.

Apart from these sociological-psychological aspects, the very nature of expertise is misunderstood.

The progress made in science is astounding and tends to confer a divine aura on its authors, which they hold very dear (4). In this context, and adding the severe lack of philosophical education that currently exists, scientific truth tends to become The Truth (5), absolute to the point of becoming a scientistic religion, with its priests, rites, temple guardians and even ritual sacrifices (6). As a result, what is not scientific is relegated to second place, or even rejected (*"I only want scientific arguments"*, one Member of Parliament said during the French National Debate on the Environment). The non-scientific nature of expertise therefore appears as a defect, as something to be a shame to hide behind blinding references to "Sound Science". Using science does not mean practising science and not practising science is not derogatory.

We saw that toxicological tests provide results for statistical analysis which do not permit by themselves a basis for judgement. This judgement is given by an expert who, based on scientific results, introduces ideas resulting from the experiment (in terms of familiarity with the subject, how much they are used to dealing with it…) which we would have a hard time describing precisely. The corollary of this is that different experts can reach different conclusions based on the same data and that is life. This means that experts with different sensitivities should take part in evaluation and that civil society should be there together with the experts.

Instead of favouring the diversity of approaches, expert committees avoid it as much as possible, to the point of abandoning some of their missions on the pretext that another committee has already dealt with that part of the question (thus the HCB refers to ANSES for a health assessment rather than carrying out a contradictory assessment) and in appointing the same experts to different committees.

The major characteristics of scientific truth are that it is not absolute and is limited by the scope of the data: *"One of the vital principles of the scientific process is for it not to go beyond the limits of scope of the data. In practice, in biology at least, this condition is rarely strictly applied but it would be appropriate to follow it as closely as possible. Contrarily, an expert's mission (in the sense of being the person who gives an opinion on a technique), is to go beyond the scope of the data […]. This concerns an activity other than scientific*

3, Nor should be too simplistic. Some experts are very committed to reflecting on their own activity. For example there is "GM and non-GM supply chain. Co-existence and traceability: context and perspectives in Bertheau Y. (2012), a documented approach considering the issue of evaluation in its complexity and calling for civil society's involvement.

4, It has to be said that it is quite becoming.

5, See, for example: Kuntz M. *"The postmodern assault on science"* (2012) EMBO Repost do 10.1038/embor.2012.130. In this literary masterpiece, we read in particular: *"Scientific authorities are not only questioned on the quality and honesty of their experts[...], but also attacked, by post-modernism, on the scientific method and its universality"*.

6, Calame, M. (2011). *Open letter to the scientists*, Charles Léopold Mayer ed.

research, with a different truth. On the other hand the predictions made by the expert cannot really be verified given that they are not, in principle, limited by time. Therefore, they might turn out to be false but they are as a rule, never strictly corroborated. In addition, except in particular cases, the validity of this prediction is limited but this limit can only be discovered once it has been passed, without us knowing when it might occur" (7).

The different nature of these activities must be recognised and results in the need to have a multiplicity of experts' sensitivities (but is this really possible?) and in a confrontation with civil society, which is to a lesser degree moulded by university or technical training and work based on a disciplinary approach.

This subject of cultural restriction gives us the opportunity to consider that which is by far the most important: the restriction of verbal expression or restriction of relevance.

When a government wants to ban the cultivation of a GMO in their country, as happened with a number of European countries for MON810, their decision MUST be justified by new scientific factors alone. At this level of international regulation we see effects of the aforementioned scientism. Due to pressure from civil society, relayed by some (rare) politicians, we now tend to accept adding socio-economic arguments. However these socio-economic arguments must be of a scientific nature, so as not to incur the wrath of the WTO. This is the same as authorising the use of unjustifiable arguments, given that generally speaking we cannot deduce socio-economic consequences from local data (8).

Aside from the real problems invoked during different moratoria, a State can legitimately want to ban the cultivation of a GMO, for example, because of the increase in the price of basic foodstuffs and taxes which this would cause during a time of crisis, given that the State would be obliged to put measures in place for coexistence, labelling, monitoring, carrying out the necessary investments to separate crops and the production chain etc. (9).

A State might also adopt the following reasoning, which is just as acceptable or even more so but not for the European Union or the WTO: monoculture or short rotations promote an increase in relevant parasites, as well as weeds adapted to this kind of crop. As a result, in addition to other problems caused by monocultures, insecticides and herbicides are used to a larger extent. Now that the disastrous effects that these pesticides have on health and nature have become clear, pressure is being applied to curb their use.

A farmer does not easily change his method of cultivation and we understand why. However, the current need to reduce pesticide use might lead him, with the help of the public authorities, to turn to longer rotations, which avoid cultivating parasites during cultivation, amongst other benefits. Going back to longer rotations is an objective which is largely shared, even at the level of the European Commission (which just goes to show).

The introduction of GMOs producing their own insecticide, not included in pesticide-reduction programmes and/or those resistant to the application of all herbicides, represents an easy solution, hindering the efforts needed to move towards sustainable agriculture. A political decision (in the noble sense of the term) could be made as a result, however the European Union and the WTO would find this unacceptable.

7, Jacquemart F. (201 2) *« Responsabilité implicite du scientifique »*, (The implicit responsability of the scientific), http://giet-info.org/articles.php?lng=fr&pg=12

8, What is at stake in the refusals of different French governments, of both the left and right, is the acceptance of relaxing GMO authorisation procedures against the possibility of refusing the cultivation of a GMO in the country for socio-economic reasons ("subsidiarity").

9, It has been discovered that no one can put a figure on these additional costs. Despite being obvious, the argument is unacceptable because it has no scientific basis. It is not necessarily easy to prove scientifically that water is wet.

GMOs and other agricultural biotechnologies thus constitute a societal problem which needs to be dealt with, taking its complexity into account, and one which is not restricted to the direct effects on health and nature targeted by the technical evaluations. Without exhausting (far from it) this vast question, other reasons are put forward by so-called civil society.

In its recommendation on the coexistence between GMOs and non-GMOs (10), some members of the HCB's CEES (11) expressed an opinion which was then turned into an open letter, only mentioned in the press by Inf'OGM (12). It can be roughly summed up as follows:

Techno-science is presented as a self-amplifying process which evolves in an exponential way: very slow for a long time, then suddenly very quick and tending towards infinity (13). We are clearly at the stage of an almost vertical increase in this techno-scientific development, ofwhich biotechnologies are an expression . On the one hand, we cannot reach infinity in a finite world and on the other hand this process requires and engenders an increasing consumption of energy as well as mineral and biological resources (14). Apart from the energy problem, which does not have any medium-term solution without unbearably worsening attacks on the environment, mineral resources are running out. The main metals and rare earths elements used in high-tech objects in particular (but also copper, silver, zinc, etc.) will run out in the next thirty years in the way they are currently exploited (15).

Without going into a detailed description of this state of affairs, it must be pointed out that the aforementioned members of the CEES believe that we can no longer count on continuing this techno-scientific process and that, on the contrary, we must (urgently) forecast its collapse and refrain from making something as essential as food dependent on a technological process which is likely to soon come to an end (as a self-organised process) (16). Contrary to this, organic agriculture (in the version not used by the agri-food industry) disassociates itself from this dependence and at least for this reason, should be developed as a priority.

The direct effects on health and nature, which are theoretically the subject of technical evaluation (once again, as long as this is done correctly), must be studied with much more care considering that this concerns exposing consumers to products which are new to them. However, this part of the problem means we cannot see the forest for the trees, preventing us from dealing with the fundamental aspects of the dossier. It is urgent for technical evaluation to be given its rightful place: a back row seat.

10, http://www.hautconseildesbiotechnologies.fr/IMG/pdf/120117_Coexistence_Recommandation_CEES_HCB.pdf
11, R. Dujardin (Greenpeace), P. de Kochko (Friends of the Earth), F. Jacquemart (FNE), D. Evain (FNAB), M. Allès-Jardel (appointed member of the French High Council for Public Health, HCSP), J.-M. Sirvins (UNAF), G. Kastler (Confédération Paysanne), F. Veillerette .
12, « La réversibilité, condition minimale nécessaire à la coexistence », (Reversibility : the minimum condition needed for coexistence) ,Inf'OGM 1 1 6, mai/juin 201 2 ; http://www.infogm.org/spip.php?article5120
13, Additional information is available on the GIET website: http://giet-info.org/file/Texte_F Jacquemart_petit.pdf
14, Just because some resources are renewable does not mean that they are enough, in a lot of cases nowadays, renewal is smaller than consumption
15, We could extend this exploitation somewhat but it would considerably increase the financial, energy and environmental costs. Recycling is not enough to cope with increasing demand. Information on the subject is available: Del Fatti N., Bravard J.P., Vieira C. (2011) *Les ressources*, éd. Université de Saint-Etienne.
16, It is not the technique which is coming to an end but a certain process.

Annex 1

Bt proteins:
more than 600 proteins targeting invertebrates

Many genetically modified plants (GMP) produce an insecticide derived from bacterial proteins. The bacterium which naturally produces these toxins is called Bacillus thuringiensis, with the initials “Bt”. “The” bacterium Bacillus thuringiensis actually represents a very large number of different bacterial strains, each of which can produce several insecticide toxins, either in the shape of crystals attached to the bacterial spores (1) (Cry proteins, for crystal), or in the shape of water-soluble proteins excreted by the bacteria during their vegetative stage (the Vip: Vegetative insecticidal proteins) (2).

The same bacterial strain can therefore produce a Vip during its vegetative stage, then a crystal containing between one to five different toxins, which will be attached to the spores.

When an insect ingests the spore which can be found, for example, on a leaf which the insect eats, the Cry insecticidal proteins are released into the digestive tract. If the insect is sensitive to these toxins it dies, thus constituting an excellent environment for developing the bacterium.

There are more than six hundred Cry proteins currently listed and their spectrum of activity, although quite limited for one given protein, is extremely vast as a whole (3). The good specificity of each insecticidal protein (a Cry1 toxin which acts against moths, only kills certain moths and not all) make this family of Bt proteins particularly interesting for fighting against crop insect pests. That is why these proteins were classified under the term “heritage of humanity” and why particular attention is made to avoid their inappropriate use leading to resistance to them. As an aside, another interesting characteristic of these insecticides is their rapid degradation by UV rays, a characteristic no longer present in GMPs given that Bt proteins are intracellular or excreted in the ground, sheltered from light.
In the past, the classification of Cry proteins was based on their activity (Cry1 acts against moths, Cry III against beetles, etc.) Nowadays, classification is based on the degree of identity of the amino acid sequence. The list starts with Cry1Aa1, with Arabic numerals and no longer Roman ones, and currently ends with Cry72Aa1.

It is interesting to consider the way most Cry proteins act. The crystal ingested by the insect, must be made soluble. This is made possible by the high alkalinity (or even very high (4) in the case of moth larvae) of the insects’ intestine. Once it is soluble, the Cry protein is partially digested by the intestinal enzymes, leaving a protease-resistant active protein small enough to cross the peritrophic membrane, which protects the insect’s intestinal epithelium (5). These receptors are well known for Cry1, less so or not at all for other classes of Cry.
Once it is fixed, the toxin makes a hole in the intestinal epithelium and the insect dies of anorexia or septicaemia.

1, Spores are a physical form of resistance for the bacterium, which transforms itself when environmental conditions are no longer favourable to its vegetative life. When the conditions go back to being favourable, the spore produces an active bacterium.
2, There are also particular classes of toxins, such as Cyt (cytolytic toxins), with haemolytic activity or binary toxins, acting in synergy.
3, In addition to insects, some Bt proteins are active against certain mites, nematodes or protozoans, whereas parasporins, which are a category Cry proteins, can kills cancerous animal cells.
4, This can be higher than pH 12. This alkalinity allows the insect to digest properly, despite tannins in its food.
5, In GMPs, only the sequence coding for this residual active part is inserted into the genome. If the solubilisation stage is not necessary, the toxin’s action spectrum can broaden, as with MON810.

Annexe 2

(original letter is in French)

G.I.E.T. - Groupe International d'Etudes Transdisciplinaires
(International Transdisciplinary Study Group)
Bedousses Bas 30450 AUJAC – France

Aujac, June 3rd 2008
Mr Barroso, European Commission

President,

Maize MON810 is currently the subject of an authorisation renewal procedure for its all uses by the European Commission. In this context, our group would like to put a question to your Commission, concerning the toxicity tests for this GMO.

What we and consumers are asking for in terms of public health, is a reasonable assurance that MON810 is not pathogenic. Therefore it is this hypothesis which must be rejected (with of course, a reasonable risk of error).

We have noticed the lack of chronic toxicity tests, teratogenicity tests and hormonal assays which would be quite obviously necessary in the context of this question. However, this will be the subject of another question of ours.

The point which interests us here concerns sub-chronic testing on rats (90-day).

Without prejudging other criticisms of this test, we would like to ask you to answer the following question:

"When using the null hypothesis H0: the control group and test group are different; can we reject it and what would be the risks to all of the parameters studied?"

In order for things to be clear, we would like to specify that there is no need to change the protocol or restart the experiment, but only to redo the calculations with the same data.

Furthermore, and once again in an effort to be clear, we will expand on the issue below:

Toxicology and food grade tests consist of a comparison of two groups: one which has consumed the GMO food (or which receives the recombinant protein) and a control group, which consumes a food which is a close as possible but which is GMO-free (or which does not receive the recombinant protein).

Different parameters are measured for each individual in each group (weight, blood sugar, etc.) and statistical tests are carried out in order to compare the averages of each value obtained between the two groups.

The significance of these statistical tests is as follows: We decide on what we call the Null hypothesis (Noted H0). In the case of studies carried out on MON810, the null hypothesis is:

H0 = the test group (with the GMO) and the control group are identical.

A test is carried out which makes it possible to reject this hypothesis, if significant differences are observed, or not to reject it if this is not the case, and this is done with a 5% risk of being wrong (this is not an accuracy of a measure but a risk of being wrong).
- If there is a significant difference, this means that, with this risk of error, H0 can be rejected: the GMO causes a difference.
- If there is no significant difference, we conclude that no difference has been detected between the two groups, which does not mean there are none. If I see something, I confirm that it exists. If nothing is seen, this does not mean that it does not exist. This is a general rule.

It is possible to reject the null hypothesis, but never confirm it.
Nonetheless, it is not the same to not demonstrate something if we look in the right direction, or if we turn our back on it.

In the case of statistical test, it should be ensured that the protocol used gives the tests sufficient discriminatory power (>80 in practice).

Annexe 2 (suite)

It was shown (see the opinion given by the Provisional Committee for the High Authority on GMOs, which examined the MON810 in France), that the protocols used for MON810 do not have sufficient power to detect even major differences.

Therefore, toxicology studies performed on MON810 do not fulfil their objective.

Moreover, the choice of the null hypothesis is unsatisfactory. In fact, what is important to political decision-makers and the population concerned **is to know whether we can, with an acceptable risk of error, reject the hypothesis according to which the GMO is toxic.**

In the context of statistical analysis, this means that:

H0 = the two groups are different (1)

And this is the hypothesis that must be rejected.

If the tests do not allow the hypothesis according to which MON810 is toxic to be rejected, we can clearly not authorise this kind of product.

President, please accept my highest regards,
Dr. Frédéric Jacquemart
Chairman

CC: Commissioner for the Environment, Commissioner for Health, EFSA, Mr Jean-Louis Borloo and the media

(1) It must be noted that in the field of medicine, the null hypothesis currently used is based on a difference, which has to be rejected. We are following the same logic here.

Annexe 3

(original question is in French)

PARLAMENTO EUROPEO
SCHEDA DI DEPOSITO DI UNA INTERROGAZIONE PARLAMENTARE

Destinatario : CONSIGLIO
COMMISSIONE

INTERROGAZIONI ORALI INTERROGAZIONI SCRITTE
Interrogazione orale Interrogazione scri-a (Art.110)
Tempo del o interrogazione (a-100) Interrogazione scri-a prioritara (art. '10,4)

AUTORE(I) : On Luca Romagnoli
OGGETTO : Authorisation for all uses of GMO maize MON810 in Europe (de inicare)

TESTO :
Maize MON810 is currently subject to a renewal procedure for its authorisation for all uses by the European Commission. What consumers, as well as all citizens, would like, in terms of public health, is to be given reasonable assurance that MON810 is safe.

This issue concerns the (90-day) sub-chronic testing on rat.

Toxicology and food grade tests compare two groups: one which consumes the GMO food (or receives the recombinant protein) and a control group that consumes a food which is as close as possible but GMO-free (or which does not receive the recombinant protein). Different parameters are measured for each individual in each group (weight, blood sugar, etc.) and statistical tests are carried out to compare the means of each value obtained between the two groups. The significance of these statistical tests is as follows: We decide on what we call the Null hypothesis (Noted H0). In the case of studies carried out on MON810, the null hypothesis is:

H0 = the test group (with the GMO) and the control group are identical.

A test is carried out which can either reject this hypothesis, if we notice significant differences, not reject in the opposite case, and this is done with a 5% risk of error (this is not an accuracy of a measure but a risk of error).

If there is a significant difference, this means that, including this risk of error, H0 can be rejected: the GMO causes a difference.

If there is no significant difference, it can be concluded that no difference has been detected between the two groups, but this does not mean that there is no difference.

When carrying out statistical tests, it is necessary to ensure that the protocol used gives sufficient discriminatory power (>80 in practice). It was shown (see the opinion given by the Provisional Committee for the High Authority on GMOs, which examined the MON810 in France), that the protocols used for MON810 do not have sufficient power to detect even major differences. Therefore, toxicology studies performed on MON810 do not fulfil to their objective. Moreover, the choice of the null hypothesis is unsatisfactory. In fact it is more important to know whether we can, with an acceptable risk of error, reject the hypothesis of the GMOs toxicity.

We therefore ask the Commission if it can certify that genetically modified maize MON810 is not toxic, taking into account the standard risk of statistical error, that is to say: if the null hypothesis H0 is = the control and test group are different, can this be rejected and at what level of risk for all of the parameters studied? If so, can the Commission provide the calculations proving this claim?

Firma(e): Data: 04/05/2009

Annexe 4

(original question is in French)

PARLAMENTO EUROPEO
SCHEDA DI DEPOSITO DI UNA INTERROGAZIONE PARLAMENTARE

Destinatario : CONSIGLIO
COMMISSIONE

INTERROGAZIONI ORALI INTERROGAZIONI SCRITTE
Interrogazione orale con discussione (art.108) Interrogazione scritta (art.110)
Tempo del o interrogazione (a-109) Interrogazione scritta prioritaria (art. 110,4)

AUTORE(I) : Monica Frassoni
OGGETTO Toxicity tests for GMO maize MON810 (de inicare)

TESTO :
In order to authorise the GMO maize crop MON810, the European Food Safety Authority (EFSA) exclusively based its opinion on studies, provided by the applicant, in this case Monsanto. The toxicity tests provided by Monsanto include a 90-day sub-chronic test on rats. In its “Opinion on the dissemination of MON810 in France”, the Preparatory Committee for the High Authority on GMOs (PCHA), which is the official French government body with competence in the field of GMOs, concluded that the methodology used in that test did not permit any conclusion to be drawn as to whether or not there was a significant difference between the test and control groups. In other words it was not possible, on the basis of the test, to exclude the possibility of the product being toxic.

(http://www.developpement-durable.gouv.fr/IMG/pdf/avis_dissemination_mon810_09_01_2008_cle1fe248.pdf.)

(1) Is the Commission aware of the PCHA opinion?
(2) Does the Commission agree that the authorization of a product can only be justified if toxicity tests on it enable toxicity to be excluded?
(3) Can the Commission guarantee that transgenic maize MON810 is non-toxic, within the boundaries of normal statistical risk. In other words: by taking as a basis the null hypothesis H0(zero): “the control group and the test group are different”, can potential toxicity be excluded and with what risks for each of the parameters considered? If so, can the Commission forward the calculations in support of that exclusion?

Firma(e): Data:06/05/2009

Annexe 5

EFSA's "answer" to the question asked by European Members of Parliament

The two Honourable Members raise several questions regarding the 90-day rat study carried out to assess the safety on MON810 maize, however all their questions are built on a single central issue: is the rejection of the null hypothesis stating equality between the GM maize and its control sufficient to ensure safety and to exclude toxicity? Although the questions have a clear focus on statistics, EFSA wishes to address the issue from two perspectives: a biological and a statistical one.

Biological perspective

As described in detail in the scientific opinion (EFSA, 2009), during the evaluation of MON810 risk assessment the GMO Panel did not observe any biologically relevant difference between treatment groups in the 90-day rat feeding study. The only statistically significant differences observed in the rats haematology determinations were present only in female rats at low dose levels. Furthermore, these differences were all within literature reference and historical control ranges. For these reasons, the GMO Panel consider them to be spurious and of no biological relevance.

In addition, confirmation of the absence of adverse effects of dietary exposure to maize MON810 has been previously shown in 90-day feeding studies in rats supplied diets contacting maize with stacked GM maize events, in which one of the parental maize was MON810: maize MON863cMON810 under part C of Directive 2001/E8/EC (EFSA, 2005), maize MON863xNK603 under Reg. (EC) 1829/2003 (EFSA 2005).

The GMO Panel has carefully evaluated all the toxicological and nutritional data on maize MON810 and appropriate non-GMO maize control published during the last 10 years and have yet not found indication of adverse effects of maize MON810. Therefore the GMO Panel concluded in its last opinion that maize MON810 is as safe as its non-GM counterpart.

Statistical perspective

In a comparative assessment framework, as developed by OECD (OECD, 1993) a GMO is compared to an appropriate comparator in order to identify possible differences. These differences, once identified as statistically significant, are assessed for biological relevance as part of normal risk assessment practice. The identification of possible differences is normally carried out using statistical tests designed to prove difference, such as for example standard analysis if variance (ANOVA), a such traditional proof-of-difference approach the null hypothesis is always that there is equality of the GMO and the non-GM control. The outcome of the statistical test is either rejection of the null hypothesis or its acceptance.

Associated to any statistical test there is always an error (Type 1 error) which cannot be eliminated, but only minimized. Traditionally this error is seen by scientists to be = 0.005, the so-called 5% level, and it is conventionally considered as acceptable in risk assessment, and the 90-dats study on MON810 under discussion represents no exception.

By questioning the suitability of the null-hypothesis and the 5% level of the statistical test, the two Honourable Members are criticizing the proof-of-difference approach traditionally used in risk assessment and described above, rather than the specific 90-day feeding rat study performed to evaluate MON810 safety.

Annexe 6

(original question is in French)

Question by the Member of the European European Parliament, José Bové and Mr Dalli's answer
Question for written answer P-011246/2010
to the Commission
Rule 117

José Bové (Verts/ALE)

Subject: Toxicity of MON810 genetically modified maize

In 2008 the Preparatory Committee for the High Authority (PCHA) on GMOs, which had been asked by the French Government for its opinion on MON810 genetically modified maize, criticised, among other things, the European Food Safety Authority (EFSA)'s unacceptable statements concerning statistical tests used to assess the risks linked to the use of genetically modified plants.

On 19 May 2009, Monica Frassoni MEP submitted a written question to the Commission on the methodology of toxicity tests on genetically modified maize MON810 (question E3646/09).

The French Minister of State responsible, Jean-Louis Borloo, and the Minister of State for Ecology, Chantal Jouanno, also asked the Commission this question in a letter dated 22 June 2009.

In December 2009, the French High Council for Biotechnology said in its' Opinion of the HCB on the European Food Safety Authority's answers to questions by Member States on the cultivation and consumption of maize MON810' that "the EFSA has not responded to the points raised by Monica Frassoni MEP. With regard to the toxicity studies, the EFSA referred to the article by Hammond et al. (2006). This study does not show that there is a health risk, nor does it clearly show (in terms of inferential statistics) that there is no such risk. The EFSA explains how the comparison tests are carried out, with the null hypothesis H0 being that "the control group and the test group are identical". The EFSA's new recommendations for statistical procedures to be carried out when evaluating GMO-related risks take into account most of the above points: the need to carry out power analyses and use equivalence tests. The EFSA thus implicitly recognises that the abovementioned procedures are not satisfactory and that the PCHA's reservations are justified".

In the light of the opinion of the High Council for Biotechnology given in 2009, and considering that the Commission has already been asked a question on this subject but failed to provide a satisfactory answer:
- Does the Commission agree that authorisation of a product can be justified only if tests rule out toxicity?
- Can it guarantee that genetically modified maize MON810 is not toxic 'within the bounds of normal statistical risk'? In other words, taking as a basis the null hypothesis H0 'the control group and the test group are different', can potential toxicity be ruled out, and with what risks for each of the parameters considered? If so, can the Commission provide calculations in support of that statement?

Annexe 6 (suite)

Answer given by Mr Dalli on behalf of the Commission

The Commission agrees with the Honourable Member that, in accordance with the requirements of Regulation (EC) No 1829/2003

The Commission agrees with the Honourable Member that, in accordance with the requirements of Regulation (EC) No 1829/2003 (1), genetically modified (GM) food and feed must not have adverse effects on human health, animal health and the environment and can only be authorised if this is indeed the case.

In the case of MON810 maize, the genetically modified organism (GMO) Panel of the European Food Safety Authority (EFSA) concluded in 2009 that 'Maize MON810 and derived products are unlikely to have any adverse effect on human and animal health in the context of the intended uses' (2). The opinion of EFSA is providing a detailed rationale on the different scientific arguments on which this conclusion is based. In its answer to Question E3646/09 (3), the Commission had mentioned that the specific points raised by the Honourable Member on the 90-day rat study carried out on MON 810 were of the competency of the EFSA, which would provide a separate answer. The Commission sent the EFSA's answer by mail to Ms. Frassoni on 4 August 2009. The relevant extracts of the reply of EFSA which answer the questions raised by Honourable Member are provided in Annex, which is sent directly to the Honourable Member and to the European Parliament's Secretariat (4).

(1) OJ L 268, 18.10.2003.
(2) The EFSA Journal (2009) 1149.
(3) http://www.europarl.europa.eu/QP-WEB/home.jsp
(4) EFSA is an organisation that is independent from the Commission and that has been created by Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. Consequently EFSA's reply, transmitted by the Commission, is the sole responsibility of the Authority.

Annexe 7

efsa
European Food Safety Authority

EXECUTIVE DIRECTOR

Parma, 26 APR 2012
Ref. CGL/PB/EW/AC/lg (2012) **6507529**

Frédéric Jacquemart
Inf'OGM
2b rue Jules Ferry
93100 Montreuil
France

Re: Request for information on three opinions of the EFSA GMO Panel

Dear Mr Jacquemart,

Thank you for your letter asking for clarifications on the evaluation of the 90-day feeding study in rats performed in the frame of the MON810 maize risk assessment.

In response to your question whether histology slides have been directly studied by the EFSA GMO Panel, I would like to point out that this approach was not considered necessary by the Panel. The respective study was performed by a specialised pathology laboratory, following quality standards and international GLP guidance (OECD 1997). A report including the detailed histopathology incidence tables has been provided and evaluated by the EFSA GMO Panel. As explained in the EFSA's published scientific opinion on MON810 maize[1] no indications of adverse effects were observed.

Do not hesitate to contact me if you have further questions.

Yours sincerely,

Catherine Geslain-Lanéelle

[1] http://www.efsa.europa.eu/en/efsajournal/doc/1149.pdf

European Food Safety Authority – Via Carlo Magno 1/a, 43126 Parma, ITALY
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Annexe 8

Anses's answer

Anses
The Director General

Dr. Frédéric Jacquemart
Chairman of the association INF'OGM
2 bis rue Jules FERRY
93100 MONTREUIL

Subject: Answer to your letter from the 16th of August with regard to Anses 2011 report.

Dear Sir,

Following your letter from the 16th of August 2011, please find the answers to your requests below:

With regard to the data from the study analysed in the aforementioned report, we had access to them in their paper form via EFSA's extranet site, reserved for the GMO assessment bodies of Member States. As highlighted in its report (Anses 2011) (1), the applicant should provide the data in numerical form so as to simplify the additional verifications or analyses deemed necessary by the experts.

The histological slides (2) of the study analysed in the Anses report were not examined by the experts of the CES, who did not consider this test useful given that the results had not been contested and that the analysis of clinical and biological data had not revealed any differences between the GMO and control treatments which could be interpreted as the toxicity of the product studied.

As written in our letter from the 4th of August, it is only if the results are contested that the slides must be made available to a laboratory specialising in anatamopathology for new tests.

Yours faithfully,

(1) Anses report 2011 "Recommendations for carrying out the statistical analysis of data from sub-chronic toxicity studies of 90 days on rats in the context of an application for authorisation to put the GMO on the market.
(2) Around 1400 slides

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Telephone: + 33 (0)149771350 – Fax +33(0)149772626 – www.anses.fr

RECENTLY RELEASED

WITH OR WITHOUT GMOS, INTERPRETING THE LABELLING

REGULATION AND DETECTION: THE ISSUES AND AMBIGUITIES (IN FRENCH)

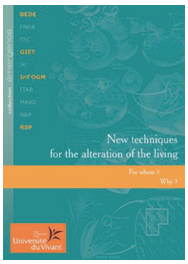
On the 1st of July 2012, the Decree defining the different "GMO-free" labels came into force for vegetable products and above all for products made from animals fed GMO-free feed, a major novelty in terms of regulation. Because of this, Inf'OGM produced a brochure which provides an exhaustive overview of French and European regulation, a detailed explanation on technical issues and an analysis of the economic consequences.

We often hear that the European Union has the "best" labeling system in the world: this is true on several fronts but it remains incomplete, particularly with regard to animals fed GMOs. And yet, the GM plants currently on the market are essentially used to feed livestock. The new French Regulation will therefore give those farmers who choose "GMO-free" products, the opportunity to promote them to consumers. Conversely, consumers can assume that if there is not this label, the animal products are from livestock which might have had GMPs in their feed. Therefore, they now have a tool which helps them to make the choice of consuming GMO or GMO-free.
Consumers will find the answers to a number of questions: What does 'GMO-free" mean exactly? Is a 0% threshold technically possible? Why do different laboratories not necessarily end up with the same results? How long does a chicken have to be fed GMO-free feed in order to be labeled as such? What does the WTO say about labeling?... In the end we have a vital tool for those who really want to understand and act on the traceability of "with or without GMOs"...

Noisette et al., "With or without GMOs, interpreting the labeling", Inf'OGM ed. July 2012, A5, 60p. 6 euros
Summary available on http://www.infogm.org/spip/php?article5166.

NEW TECHNICS OF THE ALTERATION OF THE LIVING:

FOR WHOM? WHY? (IN ENGLISH)



Inf'OGM has published in october 2011 a report (in french) on the new techniques of biotechnology. In summer 2012, Inf'OGM decided to provide the european citizens with an english version of this report. You can donwload this report on this page:
http://www.infogm.org/spip.php?article5191.

Plant genetic engineering with laboratories' techniques is a process still going on in the biotech companies' laboratories. The current commercialised GMOs come from a technique already obsolete. For transgenesis is no longer the only technique adopted by the industries to genetically modify plants. The technicians have now the choice between several techniques with names such as zinc finger nuclease technology, cisgenesis... Focusing on the risks associated with transgenesis, which allows the genetic chimera development, public debate got recently interested in older genetic engineering technique like mutagenesis. This debate on mutated plants did not occur prior to their commercialisation which happened with no legal biosafety framework. New techniques that are now coming out from laboratories require public attention. By the end of 2008, European commission requested from member states two experts to join a european working group. Its goal was to answer the following question : does GMO legislation applies to products obtained through the use of those eight techniques? In June 2011, the experts had not finished their work and no calendar was known by then. To answer this new move of technoscience, a seminar was organised by Inf'OGM in order to start thinking an independent and critical analysis. With the purpose of having a democratic debate with sufficient knowledge....

INF´OGM, THE NEWSLETTER (IN FRENCH)

A FORTNIGHTLY NEWSLETTER OF INDEPENDANT AND CRITICAL INFORMATION ABOUT GMOS

Ideal for learning the ropes about GMOs, the Inf'OGM newsletter keeps you up-to-date about GMOs in a critical, contextualized and independent way. The newsletter started in 1999. With the help of a team of specialised journalists, Inf'OGM published its 120th issue in December 2012.

This fortnightly newsletter consists of 12 pages on current affairs in France, Europe and the world, with actions carried out by local collectives; interviews and counter debates, a "thematic introduction" to deal with related issue such as seeds, other manipulations of the living or underlying questions, the regular publication of a file (situation of each plant, country genetic transformation or a data sheet on particularly thorny regulatory or scientific issues, all simply explained...), as well as news summaries and practical information (events, publications).
This bulletin is aimed at people who have been following the issue for years (politicians or activists) as well as beginners who would like to understand this sometimes stormy, yet necessary debate on vegetable and animal biotechnologies.
Subscriptions allow us to guarantee a part of Inf'OGM's self-financing and contribute to continuing its work of ensuring citizens are informed.
Inf'OGM also has a website www.infogm.org which is very regularly updated, with factual information or analyses as well as unpublished surveys.

GMO expertise:
Assessment turns its back on science

The issue of GMOs is trapped in conflictual controversies which largely hide the core of the problem, this sphere beyond the technical realm is conditioning our future. In order to solve the technical issue so as to move onto more interesting and important things, Inf'OGM has gone through some cases with a fine-tooth comb and compared the positions of experts when they acting in a scientific capacity and when they are in the capacity of experts, so as to demonstrate their contradictions. Particularly as the European Food Safety Authority (EFSA), which had been asked for several years about the harmlessness of maize MON810, finally answered but avoided the question, thus implicitly admitting its failures.

Concretely this means···selecting data, only keeping those which were favourable to industrialists, having statistical tests with such weak power that one could hardly see anything (which is what is done when one does not WANT to see anything), statements devoid of scientific bases, dishonest answers from EFSA to elected politicians and ministers who were concerned about these anomalies, the conclusion of safety based on "the weight of evidence", which means that no data really allows this conclusion to be drawn, a test developed by Monsanto and imposed by ILSI which was to show that, if it were applied in this field and following EFSA's logic, it would be very unlikely for cholera to be pathogenic for humans, in other words nothing but "Sound Science", which is how European experts like to describe what they do.

Inf'OGM says "you emphasize science, then do it properly by following its basic rules". In the meantime, activists will focus on something else, which they were too distracted to focus on due to the debate being pigeon-holed in the health question, wanted by the industry and some politicians.

In its conclusion, Inf'OMG reminds us that now what is really at stake involves the change to the cultural and ethical context currently underway.

Frédéric Jacquement is a medical doctor, medical biology specialist and has a PHD in science. He is the founding chair of GIET (International Multidisciplinary Studies Group), co-pilot of France Nature Environnement's (FNE) biotechnologies mission and has been the chair of Inf'OGM, citizen watch on GMO information, since 2010.

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January 2013

inf'OGM Veille citoyenne

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Inf'OGM is an association under Law 1901, for citizens' watch which explains global current affairs and offers a unique information service on GMOs and biotechnologies in French. Its mission is to favour and encourage the democratic debate through critical and independent information, accessible to everyone. Inf'OGM also has the aim of working to achieve real transparency in the GMO debate.

Inf'OGM is financed by the Charles Léopold Mayer Foundation for the Progress of Humankind, amongst others, which has been providing support to the entire association since its creation in 1999. The list of donors is available on the website: www.infogm.org. The donors for this brochure are listed at the beginning of this booklet.

You can find all the updates on GMOs on: www.infogm.org