EU Commission's draft GMO Regulation Charter for the GM industry

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Contact: claire.robinson@earthopensource.org

Summary

The European Commission is planning in the next few weeks to adopt a new Regulation on the risk assessment of genetically engineered food and feed.[1]

However, the standards in the new Regulation, currently in draft form, are too weak to protect human and animal health and the environment from the effects of GM crops.

If adopted, the draft Regulation will undermine the existing GMO Regulation 1829/2003[2] that was democratically established by the European Parliament and Council. It will formalize a weak GMO risk assessment in line with industry lobbying and industry-friendly decisions by the European Food Safety Authority (EFSA).

The draft Regulation directly contravenes the conclusions of the EU Environment Council, which in 2008 put forward member states' demands that the EU risk assessment of GMOs be strengthened in order to protect human and animal health and the environment.[3] The draft Regulation does the opposite, weakening safety assessment and in effect betraying the intent of the Council.

We recommend that the draft Regulation should not be adopted in its current form for the following reasons:

1. It does not mandate rigorous toxicological testing of GM crops, such as long-term, multigenerational, and immunotoxicity tests, and in vitro tests on human cells, but only stipulates a 90-day medium-term feeding trial. This is in spite of recent research showing that a GM maize, NK603, which EFSA judged to be as safe as non-GM maize EFSA and which is approved for food and feed in the EU, caused cancerous tumours, increased mortality, and organic damage in rats during a long-term 2-year feeding study.[4] The 90-day feeding trial commissioned by Monsanto to gain regulatory approval failed to detect any of these highly harmful effects, and thus largely contributed to the decision to falsely classify NK603 maize as safe for European citizens and livestock to eat.

2. It places the industry-generated but unscientific concept of comparative assessment/substantial equivalence at the basis of GMO risk assessment, contravening the requirements of the democratically established GMO Regulation 1829/2003. This marks an attempt by the Commission and the EFSA to move the

EU towards the weak GMO regulatory regime of the US. Independent, peer-reviewed scientific research has repeatedly demonstrated that GM foods are not substantially equivalent to non-GM foods but often differ in composition in unintended ways and can be more toxic or allergenic than non-GM foods.[5] The Commission's proposed comparative assessment is far too superficial to detect these unintended differences in the GMO that arise from the genetic engineering process. This is clearly demonstrated by the new long-term feeding study on NK603 maize.[4]

3. It allows industry and regulators to dismiss any statistically significant changes found in the GM crop as not "biologically relevant", without further in-depth empirical investigations, even though no rigorous standard has been set for what "biologically relevant" means, and no system has been established for determining whether any given effect is or is not "biologically relevant".

4. It does not mandate a systematic series of tests to gather empirical data on the GM crop's genetic stability, metabolic profile, or toxicity. Nor does it mandate tests to assess whether environmental stressors might trigger the GMO plant to produce toxic or allergenic molecules.

5. It contains problematic wording that could be used in future to justify waiving even the weak 90-day feeding trial. While this test is insufficient in itself, if it is the only toxicological test done on GMOs, there must be no possibility of waiving it.

6. It allows stacked trait crops to evade toxicological testing in spite of the risk of interactive effects between the different traits and with the pesticides associated with GM crops. Instead, it wrongly assumes that a stacked event is safe if the single events comprising it are judged to be safe.

7. It enables risk to be hidden by widening the range of comparators for GM crops beyond the non-GM isogenic (genetically identical) or near-isogenic variety. This runs counter to sound scientific practice as well as contravening EU Directive 2001/18. It will introduce irrelevant data that will mask, not reveal, changes caused by the genetic engineering process. When applied to stacked traits, this practice takes risk assessment even further out of the realm of empirically derived data and into the realm of assumption and speculation.

8. It continues to base the risk assessment on industry-generated data. Combined with the lack of independent research on GM products, this system favours bias.

Recommended changes to the draft Regulation:

1. Rigorous toxicological tests must be mandatory. These must include long-term (at least 2 years in rodents) and multigenerational feeding trials, as well as tests for immunotoxicity and in vitro tests on human cells.

2. The concept of comparative assessment – examining levels of major plant constituents, such as fat, carbohydrate, protein, and trace minerals in the GM plant and non-GM comparator and using the results to affirm safety – must be removed from the draft Regulation and its proposed use as the core risk assessment method

for GMOs must be abandoned.

3. A system for working out whether statistically significant changes are biologically relevant must be finalised. It must not be left to industry and regulators to dismiss without rigorous justification statistically significant differences found between the GM plant and the corresponding non-GM isogenic line, or effects found in test animals, as not “biologically relevant”. The regulation should not allow industry and regulators to shift their definition of “biologically relevant” from case to case as convenient.

4. A series of mandatory tests must be established for each GMO in order to gather empirical data and assess whether unintended changes have resulted from the genetic engineering process or from interactions between the GMO and its environment. In cases where a comparator is needed, only the non-GM isogenic or near-isogenic plant must be used. Unrelated and historical varieties must not be used as they introduce irrelevant and confounding data that will mask changes brought about by the genetic modification process.

5. The problematic wording that allows for the possibility that even the 90-day feeding trial might be waived in future must be removed.

6. For stacked trait crops, toxicological testing of the entire plant must be mandatory. It is insufficient to assume that the behaviour of the stacked variety can be extrapolated from a linear combination of the behaviours of the individual varieties. Testing must include pesticide residues in combination with the GMO.

7. All wording that allows comparators other than the non-GM isogenic or near-isogenic parent plant to be used in risk assessment of GM plants, such as “the range of natural variation”, must be removed and only the non-GM isogenic or near-isogenic variety must be used as a comparator. This applies also to stacked trait crops or products of complex genetic engineering. We challenge claims that such a comparator cannot always be made available.

8. The practice of basing the risk assessment on industry-generated data must end. Industry must pay into a publicly administered fund that will be used to commission tests from independent laboratories. Industry must also contribute funds to independent research on risks of the GM plant. The EU should introduce a commission including representatives of civil society and consumer groups to ensure that the money is spent in the public interest.

Vote behind closed doors

The Commission’s new draft Regulation will be voted on behind closed doors by the Standing Committee on the Food Chain and Animal Health (SCFCAH).

The SCFCAH’s members are appointed by the member state, often the ministry of agriculture, and are empowered to negotiate and vote on behalf of the state. This arrangement lacks accountability in that it is difficult, if not impossible, for citizens to find out precisely who in each member state is responsible for the decision.

The vote on the new Regulation will take place on an undisclosed date, according to health and consumer directorate DG SANCO, some time "after the summer"[6] – possibly as soon as mid-September or October.

There has been no public consultation about this draft Regulation. Earth Open Source was told by Ms Sabine Pelsser of DG SANCO that two meetings of the Advisory Group of the Food Chain and Animal Health were held to discuss the draft Regulation on 7 July 2007 and 14 February 2012. Ms Pelsser stated in an email, "All interested parties were invited including NGOs like Friends of the Earth and Greenpeace".[7]

However, an invitation-only meeting notified only to parties known at the time to be interested is not enough to ensure democratic input from all relevant stakeholders into this draft Regulation, which, if adopted, will have far-reaching implications for public health and environmental safety.

A full public consultation should be carried out within the member states and member state representatives in the SCFCAH should vote not to adopt it until it has been revised in accordance with the intent of the EU's existing GMO regulations, the demands of the Environment Council, and the principles of rigorous science.

Misleading title of draft regulation

One reason why the new regulation may have passed "under the radar" and gone largely unnoticed by policymakers, members of the European Parliament, and some environmental and civil society organisations, may be its innocuous title: "Commission implementing Regulation… in accordance with Regulation (EC) No 1829/2003 of the European Parliament and of the Council".

The title suggests that the Commission has drafted the Regulation to uphold and fulfill the intent of the existing EU Regulation 1829/2003, the basic legislation in the EU that stipulates how GMOs are assessed for safety.

But the title of the draft Regulation is misleading. It could more accurately have been worded: "Regulation undermining Regulation (EC) No 1829/2003 of the European Parliament and of the Council". This is because the draft Regulation contravenes key principles of the existing Regulation 1829/2003 – as well as Directive 2001/18 and the demands of the Environment Council, as explained below.

WHAT'S WRONG WITH THE DRAFT REGULATION?

1. The draft Regulation does not require rigorous toxicological testing

The need for rigorous toxicological testing of GM plants is clear, as feeding studies on animals comparing GM and non-GM equivalent diets show that the GM foods are not "substantially equivalent" to non-GM foods but have unexpected toxic or allergenic effects (see Annex II).

Yet the draft Regulation only requires a 90-day feeding trial with single-event (single trait) GMOs. While this is an improvement on existing legislation and practice, which does not make this 90-day trial mandatory, it is still inadequate because an already definitive body of scientific evidence demonstrates that 90-day feeding trials are too short to reveal long-term (chronic) effects and that long-term studies are needed.[8] [9] [10] [11] Ninety-day rodent trials are defined by the Organisation for Economic Cooperation and Development (OECD) as subchronic or medium-term only. The 90-day test fails to examine effects from exposures during vulnerable life phases, such as development in the uterus, infancy, and old age.

The inadequacy of the 90-day trial is demonstrated by a newly published 2-year feeding study on glyphosate-tolerant GM maize NK603 – a maize that EFSA has declared as safe as non-GM maize and the EU authorities have approved for use in food and feed in the EU.[4] Rats were fed the GM maize NK603, grown with and without Roundup treatment. In addition, Roundup alone was tested. Exposures were maintained long-term, over a 2-year period. Controls were fed a diet containing the non-GM isogenic maize. The findings showed that the GM maize, and Roundup at concentrations below officially set safety limits, can cause tumours and multiple organ damage and lead to premature death. Importantly, the serious effects of tumours and premature death were not detected in the 90-day rat feeding trial that the European Commission used in its earlier safety assessment of NK603 maize.

In the new research study, all treated groups had significantly higher mortality. By the beginning of the 24th month, 50–80% of female animals in all treated groups had developed tumours, with up to three tumours per animal, whereas only 30% of controls were affected. The Roundup-treated groups showed the greatest rates of tumor incidence, with 80% of animals affected with up to three tumours for one female, in each group. The first large detectable tumours occurred only at 4 and 7 months into the study in males and females respectively and the majority of tumours were only detected from 18 months onwards. So 90-day trials would fail to detect all these tumours.

The study also showed the inadequacy of the comparative assessment and indeed the entire GMO risk assessment as performed by EFSA:

- The study showed that contrary to EFSA's claim, GM NK603 maize is not "equivalent" to its non-GM isogenic counterpart – meaning that the comparative assessment performed by EFSA failed to detect important differences in the GM maize, the full biological effects of which were only revealed through long-term tests performed by independent scientists.

- The study showed that EFSA's view that NK603 maize is equivalent to and as safe as conventional maize and "unlikely to have an adverse effect on human and animal health" is scientifically unjustifiable. Increased tumours and mortality are clearly adverse effects.[12] [13]

The principles and concepts that EFSA used in coming to the erroneous conclusion that NK603 is safe continue today as the basis of EU GMO risk assessment, and the draft Regulation proposed by the Commission weakens the risk assessment process even further.

Even the inadequate 90-day trial is under threat

In spite of the above facts, the draft Regulation appears to foresee a situation in which even the inadequate 90-day feeding trial for single events is not required. It says that the 90-day trial should be "*requested*" (not "mandated" or "required") "*for the time being*" (Preamble, paragraph 11). This form of wording, unusual in a legal document because of its vagueness, only makes sense in the context of an attempt to create a loophole for the abolition of the 90-day trial. This loophole should be removed from the Regulation.

Our interpretation of this problematic wording is confirmed by an EFSA Opinion of 2008 on the role of animal feeding trials in the safety assessment of GMOs. EFSA says (7.5.12) that if substantial equivalence has been demonstrated – this will necessarily be through the inadequate comparative assessment – feeding trials are not needed:

> "*In cases where molecular, compositional, phenotypic, agronomic and other analyses have demonstrated equivalence between the GM plant derived food and feed and their conventional counterpart, except for the inserted trait(s), and results of these analyses do not indicate the occurrence of unintended effects, the performance of animal feeding trials with rodents or with target animal species adds little if anything to the overall safety assessment, and is not recommended.*"[14]

EFSA also claims that 90-day trials are long enough to identify toxicological effects that could result in more severe adverse effects from long-term (chronic) exposure.

EFSA's Opinion is scientifically unjustifiable in the light of the newly published research showing that the GM maize NK603 caused tumours, premature death and organ damage in 2-year feeding trials,[4] when the same maize had passed EFSA's weak comparative assessment without a problem and the findings of industry's 90-day trial raised no objection from EFSA.[12] [13]

Indeed, EFSA's unscientific approach is confirmed by its additional statement that the 90-day feeding trial adds little to the safety assessment "except for added confirmation of safety". This suggests that EFSA has already decided GMOs are safe and is only looking for confirmation of their assumption – an unscientific and biased approach. Research by Testbiotech shows that EFSA formed its stance on animal feeding trials under the heavy influence of the industry lobby group, the International Life Sciences Institute (ILSI).[15]

Even prior to the appearance of the new research on NK603, EFSA's Opinion ignores the fact that GM plants have often been found to be compositionally different from the non-GM

isogenic variety in unintended ways (see Annex I) that cannot be ascertained without in-depth toxicological, biochemical or other molecular analyses. Also, EFSA ignores the fact that unintended changes and differences in toxicological effects have been found in other studies on GMOs (see Annex II).

The wording in the draft Regulation gives EFSA leeway to follow the course for which it has already laid the ground in its scientifically inaccurate Opinion: allowing industry to avoid conducting any animal feeding trials at all.

Additional weakness of the draft Regulation include the fact that it does not require testing for immunotoxicity in all cases. It also does not require multigenerational tests or tests on reproductive effects. This is a serious omission, as a study found that rats fed over three generations on a GM Bt maize variety resistant to corn borer (it is unclear whether this was a commercialized variety) suffered damage to liver and kidneys and alterations in blood biochemistry. The authors concluded, "long-term feeding studies with GM crops should be performed".[10]

Finally, the fact that the draft Regulation continues to allow industry to perform its own toxicological testing is unacceptable as it enables bias. It is clearly established that funder bias affects the outcome of scientific research studies, including those on GMO safety.[16] [17] [18] [19] [20]

Recommendations:

Toxicological tests must be mandatory for every GMO that is considered for commercialization. They should include long-term (at least 2 years in rodents) and multigenerational tests. The studies should use test group sizes that ensure adequate statistical power to generate definitive data. Exposure should be performed during development in the uterus, infancy, and old age. Immunotoxicity tests should always be performed.

The wording in paragraph 11 of the Preamble should be revised to close the loophole that could allow even the inadequate 90-day animal feeding trial to be waived in the future. The words "for the time being" should be removed. The word "requested" should be replaced with "required".

While industry should pay the costs of toxicological testing of GMOs, a barrier must be maintained between it and EFSA. Industry should pay money not to EFSA but into a publicly administered fund. The administrators of the fund should then commission tests from independent laboratories.

2. The draft Regulation makes comparative assessment/substantial equivalence the basis of GMO risk assessment

"Comparative assessment" is a cosmetic rewording of the discredited concept of "substantial equivalence.", which assumes that the GM plant is no different from plants derived from traditional breeding, apart from the intended GM trait. Both concepts have been promoted by industry interests to smooth the path of GMOs into the marketplace.

The concept of comparative assessment is based on the assumption that by examining levels of major plant constituents, such as fat, carbohydrate, protein, and trace minerals and by examining gross anatomical and agronomic properties of a GMO, one can conclude whether the GMO is comparable or substantially equivalent to the original non-GM variety from which the GMO was derived. If no differences in these superficial parameters are observed, between the GM crop and the non-GM plants to which it is compared, then the GM plant is assumed to have safely passed this part of the risk assessment.

However, scientific evidence does not support the concept of comparative assessment. GM plants are fundamentally different from non-GM plants: the genetic engineering process is designed to bypass species barriers and override the host plant's regulatory system in order to enforce specific biological changes. This is likely to create unintended differences in the composition and toxicological effects of the GMO.

Indeed, when subjected to analysis, GM plants have been shown to be compositionally different in unintended ways from non-GM plants. GM plants have also been shown to have unexpected toxic or allergenic effects when fed to laboratory animals, or to have altered nutritional value (see Annexes I and II). These differences have been found even in commercialized GM varieties. The recently published study on NK603 maize is just the most recent example of evidence to this effect.

The only way to reliably detect such unintended differences is to subject the GM plant to investigations such as animal toxicological tests and stress tests prior to approval. These must include toxicological tests on the plants after they have been subjected to environmental stressors, since such stressors can cause the plant to produce compounds that may be toxic or allergenic. Comparative assessment is highly unlikely to detect these kinds of toxic and allergenic effects and cannot provide a consistently reliable and effective assessment of the safety of GMOs.

In addition, no limits have ever been set to decide what level of difference would have to exist between a GM plant and its non-GM isogenic comparator in order for it to fail the comparative assessment.

The process is also prone to data gaps. In any comparative assessment you can only find what you are looking for and unexpected differences are likely to pass unnoticed.

The draft Regulation undermines the scientific credibility of the risk assessment

The existing GMO Regulation 1829/2003 is rightly dismissive of the concept of substantial equivalence – and, by implication, the synonymous concept of comparative assessment, because (Preamble, paragraph 6):

> *"Whilst substantial equivalence is a key step in the procedure for assessment of the safety of genetically modified foods, it is not a safety assessment in itself."*[2]

Regulation 1829/2003 adds that a notification process for GM foods based on the concept of substantial equivalence "should be abandoned in respect of genetically modified foods".

But the draft Regulation, in direct contradiction to Regulation 1829/2003, makes comparative assessment the core element of GMO risk assessment in Europe. Not only does the draft Regulation call comparative assessment "*the starting point to structure and conduct the risk assessment*" (1.3) – it also allows for the possibility that it may be both the beginning and end of the GMO safety assessment (Preamble, paragraph 10):

> *"Depending on the characteristics of the genetically modified plant and on the outcome of that first set of studies, the EFSA guidance indicates that it may be necessary to perform additional studies."*

The inclusion of this wording fatally undermines the scientific credibility of the risk assessment. Its implication is that GM plants that pass the very weak initial screening may not be subjected to further detailed investigations. The wording leaves room for industry and regulators to waive further tests.

Comparative assessment becomes comparative safety assessment

Our interpretation that the new draft Regulation opens the door for comparative assessment becoming both the beginning and end of the risk assessment is confirmed by the draft Regulation's addition of the crucial word "safety" to the term "comparative assessment", which has now become "comparative safety assessment".

The addition of this one word may seem insignificant. But it marks a radical departure from, and contradiction of, Regulation 1829/2003's principle that substantial equivalence (and thus comparative assessment) "*is not a safety assessment in itself*".

Effectively, the new wording allows industry and EFSA to disobey existing law and treat the comparative assessment as a stand-alone safety assessment. Industry could be allowed to waive further tests on the GMO, based on the outcome of this scientifically unsound upstream screening step.

These developments – placing the comparative assessment at the core of GMO risk assessment and making it into a "safety assessment" by itself – take the EU down the US route of carrying out the most superficial GMO risk assessments possible.

The comparative assessment should not be confused with the practice of testing GM plants for toxic, allergenic, or environmental effects using the non-GM isogenic/parent plant as a comparator or control. The latter is a scientifically rigorous procedure that, unlike the comparative assessment, is a means of gathering empirical data on the impact of the GMO on the health of the consumer.

Industry's central role in designing GMO risk assessment in the EU

Since GM foods were first introduced in the US in the early 1990s, industry interests have promoted the concept of substantial equivalence, which was later renamed comparative assessment, which in turn became comparative safety assessment.

The process was managed largely through the medium of the industry-funded lobby group ILSI (International Life Sciences Institute), which is sponsored by the major GM crop companies, Monsanto, Bayer, Dow, and Syngenta. ILSI affiliates became core operatives within the European Food Safety Authority (EFSA) committees that were responsible for formulating and adopting the concept of comparative assessment as a central element in the EU's risk assessment of GM crops.

This history is detailed in a report by the scientific group Testbiotech, "European Food Safety Authority: A playing field for the biotech industry".[15] The relevant points are summarized below.

The concept of comparative assessment is based on the concept of substantial equivalence, developed by industry and the Organisation for Economic Cooperation and Development (OECD) in 1993.[21]

Comparative assessment was first discussed in 2000 in a joint working group of FAO and WHO,[22] chaired by Harry Kuiper, who has been a central figure within the EFSA GMO assessment structures since their inception. Between 2001 and 2003 Kuiper and his colleagues, Gijs Kleter and Esther Kok, published several papers in scientific journals promoting the concept of comparative assessment as a central element in the risk assessment of GM plants.[23] [24] [25] [26]

From 2001, Kuiper, Kleter and Kok worked together in an ILSI task force on food biotechnology. At that time, the members of the task force were from the following companies: Cargill, Monsanto, Renessen, Dupont/Pioneer, Bayer CropSciences, Syngenta, and Dow AgroSciences.[27] The head of the task force was Kevin Glenn from Monsanto.

In 2003 Kuiper became the head of EFSA's GMO Panel and Kleter joined the panel as a staff member, as did Suzy Renckens, who in 2008 created a public controversy when she left EFSA for a job at Syngenta.

Also in 2003 Kuiper and Kok co-authored a paper on the risk assessment of GM plants that redefined substantial equivalence as comparative assessment.[23] In 2010 Kok too joined EFSA as an expert on GMO risk assessment.[28] In their paper, Kuiper and Kok freely admitted that the concept of substantial equivalence remained unchanged and that the purpose of the name change was in part to deflect the "controversy" that had grown up around the term. As they explained in their abstract:

> *"Since the first discussions on strategies to assess the food safety of genetically modified (GM) crop plants, assessment of GM plants and derived tissues has been based on comparisons with their traditionally bred counterparts. This was termed the Principle of Substantial Equivalence. However, implementation of the principle led to controversy and hampered the precision of the actual safety assessment. Here, we propose the principle be rephrased into the Comparative Safety Assessment strategy."*[23]

At the same time that Kuiper and Kok published their 2003 paper, they were part of an ILSI task force working on designing GMO risk assessment.[15] In 2004 Kuiper and Kok co-authored an ILSI paper on the risk assessment of GM foods, which defined comparative

safety assessment. The other co-authors included representatives from GM crop companies that sponsor ILSI, including Monsanto, Bayer, Dow, and Syngenta.[27]

The team around Harry Kuiper and Suzy Renckens worked on the EFSA guidance document for the risk assessment of food and feed derived from GM plants.[29] Comparative assessment was a crucial element of this scheme.

EFSA has since promoted the concept in its guidance documents on assessment of environmental risks of GM plants[30] and of risks posed by food and feed derived from GM animals,[31] as well as in a peer-reviewed paper on the safety assessment of GM plants, food and feed.[14]

Now, the EU Commission has incorporated the industry-generated concept of the comparative safety assessment into the new draft Regulation on GM food and feed (1.3, 3.2.2).[1]

The above history shows that comparative assessment is a concept developed not by independent scientific consensus but by a narrow clique of industry affiliates.

Dalli responds to concerned MEPs

In January 2012 concerned Members of the European Parliament wrote to Health and consumer affairs Commissioner John Dalli about problems with the draft Regulation. They protested about the draft Regulation's inclusion of substantial equivalence/comparative assessment against the stipulation of Regulation 1829/2003 that it "should be abandoned". The MEPs were concerned that comparative assessment "might allow a GM food or feed to bypass the normal safety and nutritional assessment on the basis of flawed data."[32]

In his reply, Dalli wrote that the MEPs were misinterpreting Regulation 1829/2003. He stated that 1829/2003 intended that the *notification procedure* for GM foods under the old Regulation 258/97 should be abandoned, due to being superseded by 1829/2003 – not that *substantial equivalence* should be abandoned.[33]

In our view, this is a disingenuous and possibly illegal argument. The first and key reason that 1829/2003 gives for abandoning the procedure stipulated in 258/97 is that "*substantial equivalence… is not a safety assessment in itself*." Regulation 1829/2003 goes on to elaborate on reasons why the procedure in 258/97 should be abandoned –

> "*In order to ensure clarity, transparency and a harmonised framework for authorisation of genetically modified food.*"

Our interpretation of this wording is that substantial equivalence is not compatible with clarity, transparency, or a harmonized framework for GMO authorizations.

So for the draft Regulation to make comparative assessment a core part of the risk assessment, and the key step that decides not only the form and extent of further investigations, but if they take place at all, is against the intent of Regulation 1829/2003.

Commissioner Dalli also claimed in his letter that the comparative assessment

"*allows the identification of all the differences (intended and unintended) potentially created by the genetic modification.*"[33]

While Commissioner Dalli adds that "all these differences are then investigated in detail", he seems unaware of the fact that if the comparative assessment claims to find no significant differences, then no further investigations will be carried out.

It appears that Commissioner Dalli has been provided with an over-simplified and inaccurate interpretation of comparative assessment that ignores rigorous scientific principles.

Commissioner Dalli also makes the point that the Commission has come under pressure from animal welfare groups and some member states to reduce animal testing.

We sympathise with the aim of such groups to reduce animal suffering. But as long as society continues to release potentially toxic substances into the environment and food supply, and in vitro test methods are still unable to detect all possible harmful effects of such substances, animal testing will be needed. This is in order to prevent far more widespread suffering and mortality in the animal and human population in general resulting from exposures to inadequately tested substances.

In the absence of rigorous controlled animal tests on GMOs, pesticides, and chemicals, the entire animal and human populations in effect become the guinea pigs for inadequately tested and potentially risky substances – with the important difference that unlike tests under laboratory conditions, no one is controlling the variables or monitoring the results.

The choice is not between rigorous animal testing and reducing suffering of experimental animals, but between rigorous animal testing on a few hundred experimental animals and putting at risk the 500 million people of the European Union. The Commission needs to make this clear to animal welfare groups, which are increasingly being drawn into industry lobbies to ask for reduced animal testing.

Recommendations:

Remove the concept of comparative assessment from the draft Regulation and abandon its use as a core risk assessment method for GMOs. The wording cited above from Preamble, paragraph 10, must be removed as it allows the comparative assessment to form the beginning and end of the risk assessment. This undermines the central purpose of the risk assessment, which is to identify unexpected risks arising from the genetic modification process. It will ensure that the risk assessment will be unlikely to find unexpected differences arising from the GM process and thus the attendant risks.

In place of the comparative assessment, mandatory tests should be performed on each GMO in order to gather empirical data and detect unintended changes that may have resulted from the genetic engineering process or from interactions between the GMO and its environment. Tests should include:

- In vitro tests on human cell cultures.

- Rigorous, long-term and multigenerational toxicological tests, comparing the GM crop with the non-GM isogenic/near isogenic crop as feed for test animals. The approach of using non-GM isogenic comparators is feasible, even for GM crops that contain stacked events or the products of complex genetic engineering.
- Metabolic profiling.
- Protein profiling.
- Gene expression profiling.
- Genetic stability tests.
- "Stress tests", in which the GM crop and the non-GM isogenic crop are subjected to challenges in the laboratory that it might encounter in the field, such as exposure to crop diseases and simulated adverse weather conditions. A recent study on GM wheat shows that changes in environmental conditions, such as whether the crop is grown in the greenhouse or field, or the application of fungicide or fertilizer, can dramatically affect the performance of a GM crop.[34] Such changes could increase the risk of it being toxic, carcinogenic, or allergenic, or of causing environmental harm.

In tests where a comparator is used, the non-GM isogenic or near-isogenic plant must be used, as they are the only scientifically valid comparators.

3. The draft Regulation allows significant differences in the GM plant to be dismissed as not "biologically relevant"

The draft Regulation compounds the problems with comparative assessment by allowing industry and regulators to dismiss statistically significant differences in the composition of the GM plant or the effects of the GM plant on test animals as not being biologically relevant (1.3.2.2) without further empirical investigation. This is problematic from several points of view:

- No consistent standards and procedures to judge biological relevance in the context of GMO risk assessment have been defined, either legally or scientifically. EFSA's Opinion on the topic leaves it up to industry to decide what is biologically relevant and without standards and procedures, industry is free to change its parameters for each case.[35]

- Whether a statistically significant compositional difference in the GM plant is biologically relevant can only be determined by further in-depth investigations, including long-term toxicological testing.

- Even if a statistically significant compositional difference in the GM plant does not have an obvious explanation that would cause it to be judged "biologically relevant", the fact that such a change has been found in some metabolite, structure or function, arising from the genetic engineering process, clearly indicates that significant, measurable changes in intermediary metabolism, physiological structure or function have occurred. It is an open question as to whether those changes may have altered other structures or functions that were not measured in the safety assessment, but which might be of great toxicological or nutritional relevance. This type of open question cannot be ignored, but must be resolved by further in-depth

investigations. This would include, most importantly, long-term toxicological and nutritional testing.

Recommendations:

- Establish a strict set of standards and procedures through application of which industry and regulators could decide whether a statistically significant difference is "biologically relevant". This term must not remain in the draft Regulation as long as it has not been defined in a scientifically rigorous manner. EFSA's Opinion on the topic is inadequate to set proper standards for risk assessment because it gives industry and regulators free rein to dismiss any statistically significant differences in the GM plant as not biologically relevant without further in-depth empirical investigation or even rigorous scientific justification.[35]

- Establish as explicit policy that when any statistically significant difference between a GM plant and its near-isogenic non-GM counterpart is observed, that observation should be taken as a signal that other, yet undetected differences may also exist, which may be of great biological and health significance, and therefore that additional, in-depth testing is required before the GMO can be approved for commercialization. The testing to be carried out in such cases should use relevant biological systems and be sufficiently broad in scope to detect unanticipated health impacts. That means the GM plant must, at least, be subjected to long-term in vivo toxicological testing, involving exposure to the whole GM plant as well as to isolated substances derived from the whole plant, e.g. plant-derived Bt toxins (not surrogate toxins produced in GM bacteria, fungi or yeast).

4. The draft Regulation does not require toxicological testing of stacked events or of pesticide residues in combination with the GM crop

The draft Regulation does not require toxicological testing of stacked trait GM plants (GM plants which are engineered to contain several GM traits), or of the stacked crop in combination with pesticide residues. Instead, toxicological tests on each single event that went into developing the stacked event are assumed to be sufficient to assess the toxicological safety of the stacked event (2.2).

This is an irresponsible assumption, since interactive effects among stacked traits are likely. Combining several GM traits with each other and with the pesticides associated with the GM crop is likely to result in unpredictable outcomes and in some cases these interactions could be synergistic.[36] The toxicological and environmental risks of a stacked event cannot be predicted or assessed without empirical data, such as are gathered by toxicological tests. These must include the feeding of plant materials generated under conditions of environmental stress, in which novel toxic or allergenic compounds might be produced.

Industry and EFSA have produced no evidence to show that the properties of crop varieties that carry stacked events can be deduced from the properties of crop varieties that carry the individual events. Moreover, there is no scientific evidence upon which to base assumptions of safety regarding stacked trait crop varieties. The draft Regulation's willful oversight of biological reality is alone a reason to reject it.

Just as there are potential interactions between the different traits stacked into a single crop variety, there can be interactions between GM traits and pesticides that can give rise to unanticipated harm to the consumer or environment. Therefore, it is equally necessary to assess together the effects of GM traits and the pesticides with which they are used.

Recommendation:

Toxicological testing of the entire stacked trait plant and combinatorial toxicological testing must be mandatory. Pesticide residues must be included in the testing.

5. The draft Regulation's application of comparative assessment to stacked events takes risk assessment into the realm of assumption and speculation

The comparative assessment applied to single event GM crops is problematic enough, as it involves assumptions that are likely to be proved incorrect and is riddled with data gaps.

But comparative assessment applied to stacked events escalates these problems to an extraordinary degree. Assumptions are made not about a single trait but about several traits, which will almost certainly interact. So assumptions about the single events that were used to develop the stacked event are multiplied up the steps of the risk assessment. This will take risk assessment even further away from empirical data and more into the realm of assumptions and speculation.

The draft Regulation legitimizes this unscientific process by allowing irrelevant and confounding data into the comparative assessment.

The core of the problem lies in the selection of comparators. The draft Regulation states (1.3.1):

> "*In the case of stacked transformation events, it is acknowledged that it is not always possible to obtain a conventional counterpart with a genetic background which is as close as a conventional counterpart for single transformation events.*"

This statement is untrue. The stacked configuration can be bred into any variety, inbred, or hybrid that the developer chooses. Thus the non-GM isogenic comparator is the chosen variety, inbred, or hybrid line, but without the GM stacked traits bred into it. There is no reason to say that obtaining an isogenic or near-isogenic non-GM comparator is impossible. It may require additional breeding work on the part of the developer, but costs are expected in carrying out any research project.

If it is understood early on by the developer that an isogenic line will be required, they can integrate this objective into their breeding programme and it can be made available for safety testing without delaying the development program and without undue cost.

It would appear that the draft Regulation has been designed to create an excuse that developers can use to avoid undertaking the rigorous scientific comparisons that would allow credible scientific conclusions to be drawn regarding a given GM plant.

The draft Regulation even allows the use of other GM plants as comparators (1.3.1), which is equally unscientific. For further guidance, the draft Regulation refers to EFSA's 2011 Guidance document on selection of comparators for the risk assessment of GM plants.

This EFSA Guidance has come under criticism because it proposed to use GM plants as comparators for stacked events and even concluded that in some cases plants from different species might be accepted as comparators.[37]

Applying the comparative assessment approach to stacked events and allowing the use of a wide range of comparators multiplies to an inordinate degree the assumptions involved in the comparative assessment of single events.

Clearly, the comparative assessment concept breaks down spectacularly in the cases of stacked events and plants produced by complex genetic engineering. But instead of admitting this fact and throwing out comparative assessment as unscientific and inapplicable, the draft Regulation attempts to save comparative assessment by throwing out scientific method.

GM plants, least of all stacked trait GM plants, cannot be deemed safe to eat on the basis of a series of assumptions but must be proven safe through empirical data.

Recommendations:

Toxicological testing of the final stacked event, in whole plant form, must be mandatory. In addition, the tests we recommend in point 1) should be performed on the stacked trait plant.

Comparative assessment should be abandoned as an element in the risk assessment of GMOs. It must not be used as an upstream screening tool that enables the waiving of core elements of safety assessment. Nor should it be used as a basis on which to decide the extent or direction of the risk assessment as a whole.

In toxicological tests and stress tests, such as we recommend under point 1, where a comparator is required, the non-GM isogenic or near-isogenic plant must be mandated as the only valid comparators. We do not accept claims that non-GM isogenic comparators cannot be made available for stacked plants or the products of complex genetic engineering.

6. The draft Regulation enables risk to be hidden by widening the range of comparators for GM crops

Comparative assessment is a flawed basis for assessing GMO safety. Yet the draft Regulation, if adopted, will further weaken this already inadequate method.

This is because the draft regulation allows the GMO to be assessed against a broad range of comparators. When describing requirements for "equivalence" tests between the GMO and the comparator, it includes wording such as "the range of natural variation" (1.3.2.1.a) or "another test material in addition to the conventional counterpart" (1.3.2.2) that allow the

introduction of irrelevant data into the comparative assessment. This would allow historical data on plants unrelated to the GMO under examination, for example, from the industry-funded ILSI database of crop plants, to be used to claim substantial equivalence.

Substantial equivalence, or its synonym, the concept of "familiarity", could even be claimed when there were statistically significant differences between the GMO and the non-GM isogenic comparator. It has become commonplace for industry and other defenders of GMOs to dismiss statistically significant differences in the composition and toxicological effects of a GMO by claiming that the differences are within the "normal variation range" or "within the range of biological variation".

But this is a spurious argument. The logic used is similar to a drug company asking for approval of a drug with a side effect of causing patients to gain 75 pounds, by arguing that even with this weight gain the person is still within the weight range for humans.

Such an unscientific argument would rightly be disallowed. Scientific experiments are designed to exclude variables other than the single factor being tested. In the case of a drug being tested for risk assessment purposes, the single factor is exposure to the drug. In the case of a GMO undergoing comparative assessment, the factor being tested is the effect of the genetic engineering process on the plant. So conclusions must only be drawn from the data derived from within this tightly controlled experiment in which all conditions are the same except that the plant being tested has been subjected to the genetic engineering process.

If the draft Regulation is adopted, it will overturn this fundamental principle of science in the interests of easing the path of GMOs through the regulatory system.

For a full discussion of this practice and how it puts public health at risk, see Earth Open Source's report, GMO Myths and Truths, Section 3.1.4.[5]

Radical departure from existing EU legislation

Allowing the GMO to be assessed using a broad range of comparators is a radical departure from existing EU legislation. EU Directive 2001/18 requires that the comparator against which the GMO should be assessed for safety is the non-GM isogenic/parent – "*the non-modified organism from which it is derived*".[38]

Directive 2001/18 recognizes that using the non-GM isogenic/parent plant as the comparator is the only way to fulfill the purpose of the comparative assessment – to identify "*the particular potential adverse effects arising from the genetic modification*".[38]

This method is designed to exclude changes resulting from a different genetic background. So any differences in the form, growth, or performance of the GM plant are likely to be due to disruptions caused by the genetic engineering process.

It is important that the GM plant and its non-GM isogenic comparator should be grown side-by-side, so that environmental conditions are the same. It is well known that environmental conditions can influence metabolic composition and well as gene expression, both of which can influence the safety of a GM crop.

Only by controlling both genetic differences (using the isogenic comparator) and environmental differences (growing the GM crop and the isogenic line side-by-side) is it possible to exclude variables due to different environmental conditions, so that the study will detect differences in the GM plant that are due to the genetic modification process.

Historically, EFSA has obeyed Directive 2001/18 and followed the principle of requiring the non-GM isogenic/parent to be used as the comparator in its Guidances and Opinions.

Yet in a Guidance published in late 2011, EFSA departed from this practice, contravening EU legislative requirements by broadening the range of acceptable comparators. EFSA even proposed to allow the use of GM plants, rather than the usual non-GM isogenic line, as comparators for stacked events (crops containing multiple GM traits) and concluded that in some cases even plants from different species might be accepted as comparators.[37] These alternatives all breach the norms of experimental design for good science and therefore are unacceptable.

EFSA's new approach would be convenient to industry, would save industry money, and would allow industry to slip potentially unsafe GM plants into the marketplace.

It is also in line with practices that have been promoted in certain review papers, for example, by Catchpole (2005)[39] and Ricroch (2011).[40] These authors concede that there are significant differences between a GM plant and the non-GM isogenic comparator, but then introduce a wider range of distantly related, non-isogenic comparators to force the conclusion that the GM plants under examination are within the natural range of variation and thus substantially equivalent to non-GM plants. Both sets of authors recommend that this system should be adopted by regulators.

No justification is provided for the validity of comparing the GMO to these additional comparators, and no evidence is provided that efforts were made to eliminate confounding influences; on the contrary, the confounding influences are embraced as proof that this alternative approach should be adopted.

However, the approach promoted by these authors and EFSA, as well as being scientifically invalid, does not comply with EU Directive 2001/18 and thus is illegal. In addition, it is beyond EFSA's remit to propose such changes. EFSA's remit is risk assessment – not alteration of regulatory policy based on "creative" reinterpretation of EU law.

From the scientific point of view, the approach of comparing a GM crop with unrelated or distantly related varieties grown at different times and in different locations is flawed. It only serves to increase the confusing influence of external variables in the form of different environmental conditions – masking, rather than highlighting, the effects of the GM transformation.

Recommendations:

If EFSA and the new Regulation are correct in claiming that isogenic comparators are not always available (a claim that we challenge), then the comparative approach becomes patently inapplicable. It is not possible to carry out a scientifically meaningful comparative

analysis if no scientifically valid comparator exists. On this basis, there is no alternative than to abandon the method of comparative assessment as it is advocated in the draft Regulation and currently practised.

The comparative assessment should be replaced by empirical investigations described in our recommendations under point 1, using the non-GM isogenic or near-isogenic parent plant as a comparator where comparators are applicable.

In the absence of such investigations, human and animals that eat GM crops, and farmers who grow them, are forced into the role of experimental guinea pigs.

Conclusion

The draft Regulation, if adopted, will not fulfill the requirements of the existing democratically established Regulation 1829/2003. On the contrary, it will undermine the Regulation. In addition, it contravenes EU Directive 2001/18. Most strikingly, instead of responding to the conclusions of the Environment Council in 2008 that the GMO risk assessment needed to be strengthened, the proposed Regulation significantly weakens the GMO risk assessment process.

The weak risk assessment stipulated in the draft Regulation will jeopardize the health and safety of Europe's citizens and the environment, will further undermine public confidence in GMOs, and will create significant economic risks for the European food and agricultural industries.

The Commission must place an immediate stop on the progress of the draft Regulation, go back to the drawing board, and revise it to reflect current scientific knowledge, uphold European law, and fulfill the demands of the EU Environment Council.

The way in which EFSA assesses the safety of GMOs must be radically overhauled and EFSA's ties to industry and ILSI severed. Its GMO-related policies and Opinions formed under the influence of industry and ILSI must be revisited and rewritten by independent experts.

Annex I: GM plants are compositionally different from non-GM plants in unintended ways

The comparative assessment approach assumes that GM plants are not inherently different from their non-GM counterparts apart from the deliberately inserted GM traits and that they pose no special risks.

This assumption is unwarranted, based on extensive evidence to the contrary. Studies comparing GM plants with their non-GM isogenic (genetically identical) counterparts – including industry's own data submitted in applications for authorisation[41] – show that GM plants have unexpected compositional differences. Examples of such plants that have nevertheless been commercialized in the EU include:

- GM soy had 12–14% lower amounts of cancer-fighting isoflavones than non-GM isogenic soy.[42]

- MON810 GM maize had a markedly different profile in the types of proteins it contained compared with the non-GM counterpart grown under the same conditions.[43]

Such differences can result in toxic or allergenic effects or altered nutritional value (see Annex II, below, and the report, GMO Myths and Truths, section 3[5]). In addition, they show that the genetic engineering process has disrupted the host plant's genome in unexpected and unintended ways.

Annex II: GM plants have been found to be more toxic or allergenic than non-GM isogenic varieties

Feeding studies in laboratory and farm animals testing commercialized GM crops against non-GM isogenic varieties found that the GM crops were more toxic or allergenic.

- Rats were fed the commercialized GM maize NK603, with and without Roundup, and Roundup alone over a long-term 2-year period. Controls were fed a diet containing the non-GM isogenic maize. Long-term harmful effects were found from the consumption of the GM maize, as well as from exposure to Roundup at concentrations well below officially set safety limits. All treated groups had significantly higher mortality. By the beginning of the 24th month, 50–80% of female animals in all treated groups had developed tumours, with up to three tumours per animal, whereas only 30% of controls were affected. The Roundup-treated groups showed the greatest rates of tumour incidence, with 80% of animals affected with up to three tumours for one female, in each group. The first large detectable tumours occurred at 4 and 7 months into the study in males and females respectively, underlining the inadequacy of 90-day feeding trials for evaluating GM crop and food toxicity.[4]

- The above-cited study followed a re-analysis by independent (non-industry) scientists of Monsanto's own 90-day rat feeding trial data, submitted to obtain approval in Europe for three commercialized GM Bt maize varieties, MON863,

MON810, and NK603, which concluded that the maize varieties had toxic effects on liver and kidneys. The authors of the re-analysis stated that while the findings may have been due to the pesticides specific to each variety, genetic engineering could not be excluded as the cause.[8]

- A review of 19 studies (including industry's own studies submitted to regulators in support of applications to commercialize GM crops) on mammals fed with commercialized GM soy and maize found consistent toxic effects on the liver and kidneys. Such effects may be markers of the onset of chronic disease, but long-term studies, in contrast to these reported short- and medium-term studies, would be required to assess this more thoroughly.[9]

- Rats fed insecticide-producing MON863 Bt maize grew more slowly and showed higher levels of certain fats (triglycerides) in their blood than rats fed the control diet. They also suffered problems with liver and kidney function. The authors stated that it could not be concluded that MON863 maize is safe and that long-term studies were needed to investigate the consequences of these effects.[44]

- Old and young mice fed GM Bt maize showed a marked disturbance in immune system cells and in biochemical activity.[45]

- Female sheep fed Bt176 GM maize (previously commercialized in the EU, now withdrawn by the developer company) over three generations showed disturbances in the functioning of the digestive system, while their lambs showed cellular changes in the liver and pancreas.[46]

These studies are included here because they examine GM foods that are currently commercialized or have previously been commercialized in the EU. This shows that the "comparative assessment" and subsequent risk assessment steps failed to identify harmful effects of the GM crop that can be clearly linked to the genetic engineering process. The conclusion is that the risk assessment needs to be strengthened, not made weaker, as will happen if the draft Regulation is adopted.

Further animal feeding studies on GM foods that have not been commercialized in the EU but which have been shown to be more toxic or allergenic than their non-GM counterparts are summarized in section 3 of the report, GMO Myths and Truths.[5]

References

This report and supporting documents, including the draft Regulation, are available for download at: http://bit.ly/OZ3a00

1. European Commission. Commission implementing regulation (EU) No…. on applications for authorisation of genetically modified food and feed in accordance with Regulation (EC) No 1829/2003 of the European Parliament and of the Council and amending Regulations (EC) No 641/2004 and (EC) No 1981/2006. 2012.
2. European Parliament and Council. Regulation (EC) No 1829/2003 of the European Parliament and of the Council of 22 September 2003 on genetically modified food and feed. Official Journal of the European Union. 18 October 2003; 268: 1–23.
3. Environment Council of the European Union. Genetically modified organisms – Council conclusions 16882/08. Brussels. 5 December 2008.
4. Séralini GE, Clair E, Mesnage R, et al. Long term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize. Food and Chemical Toxicology. 2012.
5. Antoniou M, Robinson C, Fagan J. GMO myths and truths: An evidence-based examination of the claims made for the safety and efficacy of genetically modified crops. June 2012. http://bit.ly/O0IAQS
6. Pelsser S. Re: Query seeking information: Email communication to S. Coffey. European Commission Directorate-General Health and Consumer Protection Unit E1 - Biotechnology. 9 July 2012.
7. Pelsser S. Re: EU Comm draft legislation on GMOs: Email communication to Earth Open Source. European Commission Directorate-General Health and Consumer Protection Unit E1 - Biotechnology. 30 August 2012.
8. de Vendomois JS, Roullier F, Cellier D, Séralini GE. A comparison of the effects of three GM corn varieties on mammalian health. Int J Biol Sci. 2009; 5(7): 706–726.
9. Séralini GE, Mesnage R, Clair E, Gress S, de Vendômois JS, Cellier D. Genetically modified crops safety assessments: Present limits and possible improvements. Environmental Sciences Europe. 2011; 23(10).
10. Kilic A, Akay MT. A three generation study with genetically modified Bt corn in rats: Biochemical and histopathological investigation. Food Chem Toxicol. Mar 2008; 46(3): 1164–1170.
11. Freese W, Schubert D. Safety testing and regulation of genetically engineered foods. Biotechnol Genet Eng Rev. 2004: 299-324.
12. European Food Safety Authority (EFSA). Applications (references EFSA-GMO-NL-2005-22, EFSA-GMO-RX-NK603) for the placing on the market of the genetically modified glyphosate tolerant maize NK603 for cultivation, food and feed uses, import and processing and for renewal of the authorisation of maize NK603 as existing products, both under Regulation (EC) No 1829/2003 from Monsanto: Scientific Opinion of the Panel on Genetically Modified Organisms (Questions No EFSA-Q-2005-249, No EFSA-Q-2008-075), Adopted on 27 May 2009. EFSA Journal. 2009; 2009(1137): 1–50.
13. European Food Safety Authority (EFSA). Opinion of the Scientific Panel on Genetically Modified Organisms on a request from the Commission related to the safety of foods and food ingredients derived from herbicide-tolerant genetically modified maize NK603, for which a request for placing on the market was submitted under Article 4 of the Novel Food Regulation (EC) No 258/97 by Monsanto (QUESTION NO EFSA-Q-2003-002): Opinion adopted on 25 November 2003. EFSA Journal. 2003; 2003(9): 1–14.

14. European Food Safety Authority (EFSA) GMO Panel Working Group on Animal Feeding Trials. Safety and nutritional assessment of GM plants and derived food and feed: The role of animal feeding trials. Food Chem Toxicol. Mar 2008; 46 (Suppl 1): S2-70.

15. Then C, Bauer-Panskus A. European Food Safety Authority: A playing field for the biotech industry. TestBiotech. 1 December 2010. www.testbiotech.de/sites/default/files/EFSA_Playing_Field_of_ILSI.pdf

16. Swaen GM, Meijers JM. Influence of design characteristics on the outcome of retrospective cohort studies. Br J Ind Med. Sep 1988; 45(9): 624-629.

17. Lexchin J. Those who have the gold make the evidence: How the pharmaceutical industry biases the outcomes of clinical trials of medications. Sci Eng Ethics. Feb 15 2011.

18. Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. British Medical Journal. 2003; 326: 1167.

19. Huss A, Egger M, Hug K, Huweiler-Müntener K, Röösli M. Source of funding and results of studies of health effects of mobile phone use: Systematic review of experimental studies. Environmental Health Perspectives. January 2007; 115: 1–4.

20. Diels J, Cunha M, Manaia C, Sabugosa-Madeira B, Silva M. Association of financial or professional conflict of interest to research outcomes on health risks or nutritional assessment studies of genetically modified products. Food Policy. 2011; 36: 197–203.

21. Organisation for Economic Cooperation and Development (OECD). Safety evaluation of foods derived by modern biotechnology: Concepts and principles. OECD Publishing. 29 April 1993.

22. Food and Agriculture Organization (FAO) and World Health Organization (WHO). Safety aspects of genetically modified foods of plant origin: Report of a joint FAO/WHO expert consultation on foods derived from biotechnology, World Health Organization Headquarters, Geneva, Switzerland, 29 May–2 June. 2000.

23. Kok EJ, Kuiper HA. Comparative safety assessment for biotech crops. Trends in Biotechnology. 2003; 21: 439–444.

24. Kuiper HA, Kleter GA, Noteborn HP, Kok EJ. Assessment of the food safety issues related to genetically modified foods. Plant J. Sep 2001; 27(6): 503-528.

25. Kuiper HA, Kleter GA, Noteborn HP, Kok EJ. Substantial equivalence – An appropriate paradigm for the safety assessment of genetically modified foods? Toxicology. Dec 27 2002; 181–182: 427–431.

26. Kuiper HA, Kleter GA. The scientific basis for risk assessment and regulation of genetically modified foods. Trends in Food Science & Technology. 2003; 14(5): 277-293.

27. International Life Sciences Institute (ILSI). Nutritional and safety assessments of foods and feeds nutritionally improved through biotechnology, prepared by a task force of the ILSI International Food Biotechnology Committee. Comprehensive Reviews in Food Science and Food Safety. 2004; 3: 38–104.

28. European Food Safety Authority (EFSA). Annual declaration of interests – Esther Kok. 3 August 2010.

29. European Food Safety Authority (EFSA). Guidance document of the Scientific Panel on Genetically Modified Organisms for the risk assessment of genetically modified plants and derived food and feed. EFSA Journal. 2004; 2004(99): 1–94.

30. European Food Safety Authority (EFSA) GMO Panel. Guidance on the environmental risk assessment of genetically modified plants. EFSA Journal. 2010; 8(11): 1879–1990.

31. European Food Safety Authority (EFSA). Guidance on the risk assessment of food and feed from genetically modified animals and on animal health and welfare aspects. EFSA Journal. 2012; 10(1): 2501. [2543 pp.].

32. Arsenis K, Bove J, Chountis N, et al. Letter from MEPs to the Commission and member states on the draft GM food and feed guidelines. 9 January 2012.

33. Dalli J. Letter to Members of the European Parliament. 3 March 2012.

34. Zeller SL, Kalinina O, Brunner S, Keller B, Schmid B. Transgene x environment interactions in genetically modified wheat. PLoS ONE. 2010; 5(7): e11405.

35. European Food Safety Authority (EFSA). Scientific opinion: Statistical significance and biological relevance. EFSA Journal. 2011; 9(9): 2372.

36. Mesnage R, Clair E, Gress S, Then C, Székács A, Séralini G-E. Cytotoxicity on human cells of Cry1Ab and Cry1Ac Bt insecticidal toxins alone or with a glyphosate-based herbicide. Journal of Applied Toxicology. 15 Feb 2012.

37. European Food Safety Authority Panel on Genetically Modified Organisms (GMO). Guidance document on selection of comparators for the risk assessment of GM plants. EFSA Journal. 2011; 9(5): 2149.

38. European Parliament and Council. Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. Official Journal of the European Communities. 17 April 2001: 1–38.

39. Catchpole GS, Beckmann M, Enot DP, et al. Hierarchical metabolomics demonstrates substantial compositional similarity between genetically modified and conventional potato crops. Proc Natl Acad Sci U S A. Oct 4 2005; 102(40): 14458-14462.

40. Ricroch AE, Berge JB, Kuntz M. Evaluation of genetically engineered crops using transcriptomic, proteomic, and metabolomic profiling techniques. Plant Physiol. Apr 2011; 155(4): 1752-1761.

41. Schenkelaars Biotechnology Consultancy. GM food crops and application of substantial equivalence in the European Union. The Netherlands. Commissioned by the Dutch Foundation 'Consument & Biotechnologie'. June 2001. http://www.iatp.org/files/GM_Food_Crops_and_Application_of_Substantial_E.htm

42. Lappé M, Bailey B, Childress C, Setchell KDR. Alterations in clinically important phytoestrogens in genetically modified herbicide-tolerant soybean. Journal of Medicinal Food. 1999; 1: 241–245.

43. Zolla L, Rinalducci S, Antonioli P, Righetti PG. Proteomics as a complementary tool for identifying unintended side effects occurring in transgenic maize seeds as a result of genetic modifications. J Proteome Res. May 2008; 7(5): 1850-1861.

44. Séralini GE, Cellier D, Spiroux de Vendomois J. New analysis of a rat feeding study with a genetically modified maize reveals signs of hepatorenal toxicity. Archives of Environmental Contamination and Toxicology. May 2007; 52(4): 596–602.

45. Finamore A, Roselli M, Britti S, et al. Intestinal and peripheral immune response to MON810 maize ingestion in weaning and old mice. J Agric Food Chem. Dec 10 2008; 56: 11533–11539.

46. Trabalza-Marinucci M, Brandi G, Rondini C, et al. A three-year longitudinal study on the effects of a diet containing genetically modified Bt176 maize on the health status and performance of sheep. Livestock Science. 2008; 113(2): 178–190.