

Molecular differences between GM- and non-GM crops over-estimated?

Klaus Ammann, AF-10 2010514 opensource

klaus.ammann@ips.unibe.ch

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1. Issue

The difference between GM- and non-GM-crops has been overestimated, as soon as genetic engineering has been applied to crop breeding. The uncontested understanding among scientists and in particular in risk assessment community was that GM crops pose some novel risks, unprecedented in conventionally bred crops. This has then condensed in the United Nations Cartagena Protocol on Biosafety¹, which needs to be questioned in certain basic aspects.

¹ Cartagena Protocol on Biosafety: <http://www.cbd.int/biosafety/>

2. Summary

After an early phase of risk assessment, including the results of the Asilomar Conference on biosafety, an early divide in risk assessment basic concepts developed between Canada, the USA and Europe including a majority of UN signatory countries. Researchers like Werner Arber, based on earlier molecular insights and on his own experience in genetic engineering claim that related to molecular processes there is no difference between genetically engineering and natural mutation. This transatlantic divide can be solved with some more innovative regulatory proceedings.

3. Differences between GM- and non-GM-crops overestimated

3.1. Early phase of risk assessment

In the wake of molecular breeding, in particular with the first successes of “gene splicing”, the safety debates started soon after the discovery of the DNA structure by Watson & Crick (Watson & Crick, 1953a, b; Wilkins et al., 1953), followed by the Asilomar Conference (Berg et al., 1975; Berg & Singer, 1995) - see also some historical accounts (Chassy, 2007; Friedberg, 2007; Klug, 2004). The fascination about the novelty of transgenesis was justified, but also overwhelming, and the many unforeseen scientific breakthroughs following were unprecedented in the history of molecular biology.

Unfortunately, the enthusiasm also lashed back in an overacting in risk assessment, when the first GM crops went into production. The debate on how GM crops should be regulated, started very early with an emerging divide between regulation in the US and Great Britain, including later the whole of Europe (Bennett et al., 1986; National-Research-Council, 1989).

The seemingly absolute novelty of genetic engineering on the molecular level has been contested already in the early days of molecular biology in the 1930s and 1950s with the discovery of cellular systems for genome restructuring discovered with the classic papers of McClintock (McClintock, 1930, 1953) and with later commentaries of Fedoroff (Fedoroff, 1994; Fedoroff et al., 1995), also summarized under ‘natural genetic engineering’ (Lewin, 1983; Shapiro, 1997).

3.2. Molecular processes similar in natural mutation and transgenesis

The concept of violated intrinsic naturalness of the genomes is still erroneously maintained by proponents of organic farmers (van Bueren et al., 2008; Van Bueren & Struik, 2004, 2005; Van Bueren et al., 2003). This concept of singling out transgenity is falsified by the publications of Arber (Nobel Laureate 1978).

Genetic engineering has been brought into evolutionary perspective of natural mutation by authorities such as Werner Arber: his view remains scientifically uncontested that molecular processes in transgenesis and natural mutation are basically similar (Arber, 1994, 2000, 2002, 2003, 2004). The same claim is made with a more organismal view by Hackett (Hackett, 2002).

Arber compared designed genetic alterations (including genetic engineering) with the spontaneous genetic variation known to form the substrate for biological evolution (Arber, 2002):

"Site-directed mutagenesis usually affects only a few nucleotides. Still another genetic variation sometimes produced by genetic engineering is the reshuffling of genomic sequences, e.g. if a given open reading frame is brought under a different signal for expression control or if a gene is knocked out. All such changes have little chance to change in fundamental ways, the properties of the organism. In addition, it should be remembered that the methods of molecular genetics themselves enable the researchers anytime to verify whether the effective genomic alterations correspond to their intentions, and to explore the phenotypic changes due to the alterations. This forms part of the experimental procedures of any research seriously carried out. Interestingly, naturally occurring molecular evolution, i.e. the spontaneous generation of genetic variants has been seen to follow exactly the same three strategies as those used in genetic engineering. These three strategies are:

- (a) small local changes in the nucleotide sequences,*
- (b) internal reshuffling of genomic DNA segments, and*
- (c) acquisition of usually rather small segments of DNA from another type of organism by horizontal gene transfer.*

However, there is a principal difference between the procedures of genetic engineering and those serving in nature for biological evolution. While the genetic engineer pre-reflects his alteration and verifies its results, nature places its genetic variations more randomly and largely independent of an identified goal. Under natural conditions, it is the pressure of natural selection which eventually determines, together with the available diversity of genetic variants, the direction taken by evolution. It is interesting to note that natural selection also plays its decisive role in genetic engineering, since indeed not all pre-reflected sequence alterations withstand the power of natural selection. Many investigators have experienced the effect of this natural force which does not allow functional disharmony in a mutated organism."

Arbers numerous writings (Arber, 2000, 2003, 2004) confirm this important comparison on the genomic level of evolutionary and modern plant breeding processes. But there is of course, despite all the similarities, one major difference: whereas natural mutation acts completely in a natural time scale, that is, the mutants will need hundreds to hundred of thousands of years to overcome selective processes in nature until they really succeed and take over against their natural competitors, this is totally different with the transgenic crop products: they run through a R&D phase, and a regulatory process of an average of 15 to 20 years until being completely deregulated. But somewhere along this process they will be propagated to the millions in the field, covering in a evolutionary extremely short time span millions of hectares.

In a recent paper, (Coll et al., 2009) come to the conclusion, that Gene expression profiles of MON810 and comparable non-GM maize varieties cultured in the field are more similar than are those of conventional lines. Their bibliography supports this view with numerous peer reviewed publications.

It is therefore no surprise that a natural transgene species has been discovered in a widespread grass genus (Ghatnekar et al., 2006).

(Miller & Conko, 2004) provide important arguments supporting this view:

The authors raise also in a justified way doubts about the commonly used concept of transgenesis. In the light of pre-recombinant DNA produced in great variety by conventional breeding with thousands of foreign genes.

"In these examples of prerecombinant-DNA genetic improvement, breeders and food producers possess little knowledge of the exact genetic changes that produced the useful trait, information about what other changes have occurred concomitantly in the plant or data on the transfer of newly incorporated genes into animals, humans or microorganisms. Consider, for example, the relatively new man-made wheat 'species' Triticum agropyrotriticum, which resulted from the wide-cross combination of the genomes of bread wheat and a wild grass sometimes called quackgrass or couchgrass (Banks et al., 1993; Sinigovets, 1987) T. agropyrotriticum, which possesses all the chromosomes of wheat as well as the entire genome of the quackgrass, was independently produced for both animal feed and human food in the former Soviet Union, Canada, the United States, France,

Germany and China." See also the ASK-FORCE contributions on the web by K. Ammann 2009² on the same subject.

Recent publications demonstrate, that transgenesis e.g. has less impact on the transcriptome of the wheat grain than traditional breeding (Batista et al., 2008; Baudo et al., 2006; Shewry et al., 2007), (more details: (Ammann, 2008, 2009)).

Two figures may suffice to visualize the lower impact on transcriptome expression of transgenic crops compared to conventional ones:

Volcano plots from (Batista et al., 2008):

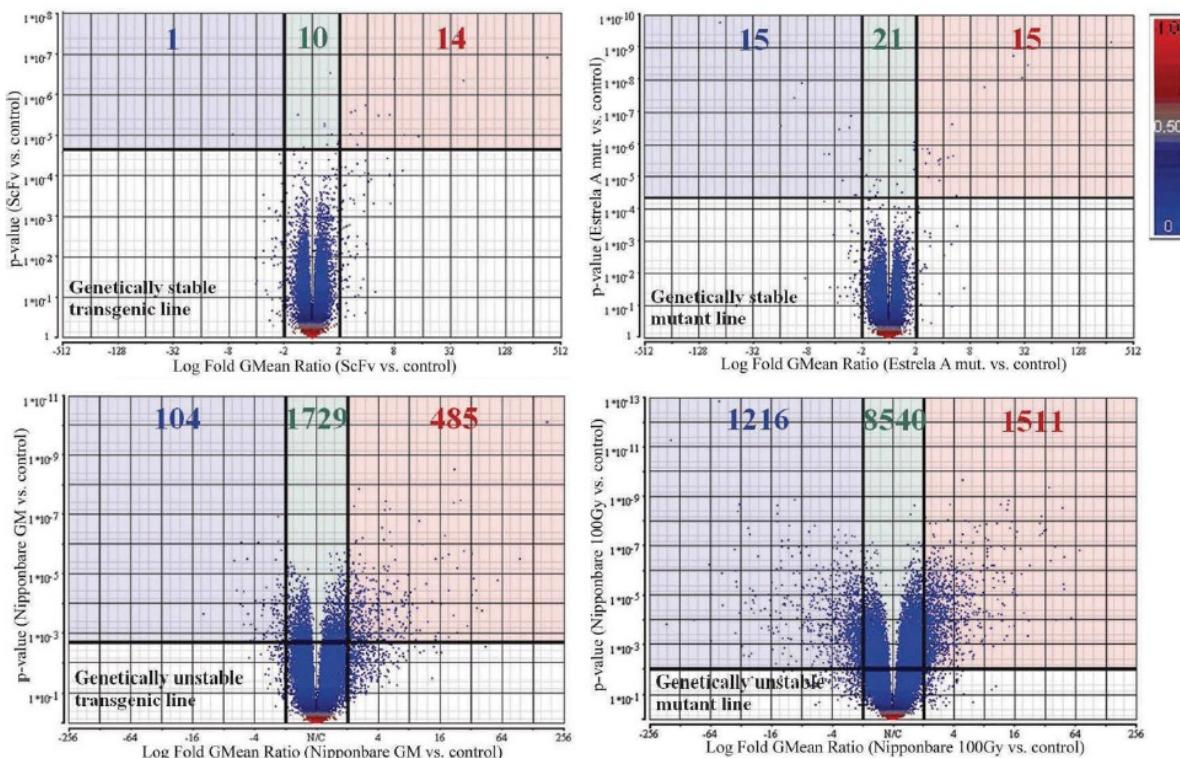


Fig. 1 Volcano plots for differentially expressed genes. Differentially expressed genes appear above the thick horizontal lines. Genes induced _2-fold are on the right of the right vertical lines, and the ones repressed _2-fold are on the left of the left vertical line. The numbers corresponding to the differentially expressed genes induced _2-fold for each experiment (red-shadowed area) are red, and those corresponding to the genes repressed _2-fold (blue-shadowed area) are blue. The green-shadowed area corresponds to differentially expressed genes that were up- or down-regulated _2-fold (green-colored numbers). Blue-colored genes are those with P between 0 and 0.5, and red-colored genes are those with P between 0.5 and 1. From (Batista et al., 2008)

² ASK-FORCE contribution K. Ammann 2009: Regulation: Misconcepts cause high costs and huge delays in regulation of GM crops: <http://www.efb-central.org/index.php/forums/viewthread/59/>

Plots from (Baudo et al., 2006)

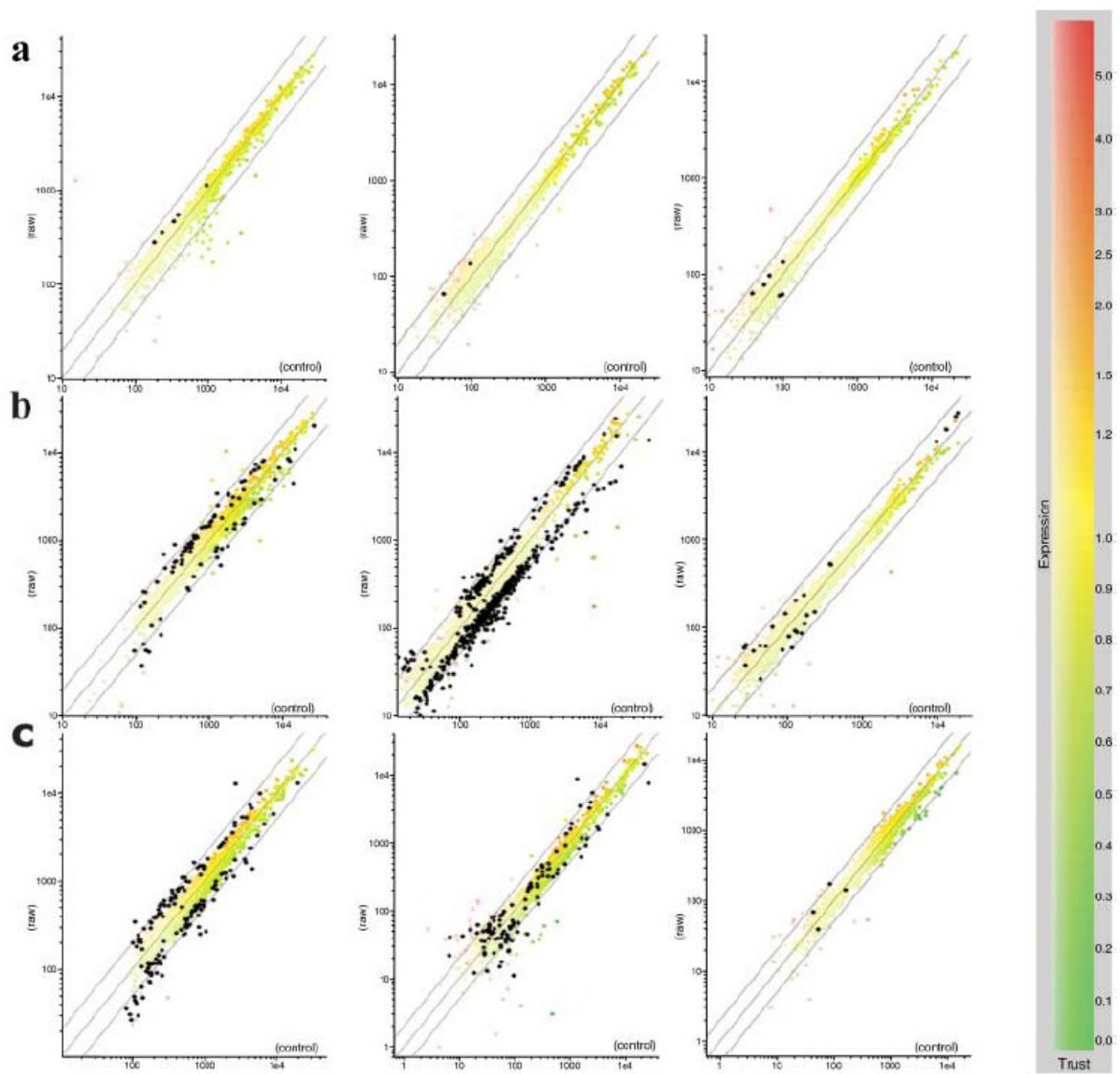


Fig. 2 Scatter plot representation of transcriptome comparisons of: (a) transgenic B102-1-1 line vs. control L88-31 line in endosperm at 14 dpa (left), 28 dpa (middle) or leaf at 8 dpg (right); (b) conventionally bred L88-18 vs. L88-31 line in endosperm at 14 dpa (left), 28 dpa (middle), or leaf at 8 dpg (right); (c) transgenic B102-1-1 line vs. conventionally bred L88-18 line in endosperm at 14 dpa (left), 28 dpa (middle), or leaf at 8 dpg (right). Dots represent the normalized relative expression level of each arrayed gene for the transcriptome comparisons described. Dots in black represent statistically significant, differentially expressed genes (DEG) at an arbitrary cut off > 1.5 . The inner line on each graph represents no change in expression. The offset dashed lines are set at a relative expression cut-off of twofold. In the adjacent coloured bar (rectangle on the far right of the figure), the vertical axis represents relative gene expression levels: reds indicate overexpression, yellows average expression, and greens under-expression. Values are expressed as n-fold changes. The horizontal axis of this bar represents the degree to which data can be trusted: dark or unsaturated colour represents low trust and bright or saturated colour represents high trust. From (Baudo et al., 2006).

In the most recent paper on transcriptomic comparison, (Kogel et al., 2010) come to the following similar conclusions:

"In summary, our results substantially extend observations that cultivar-specific differences in transcriptome and metabolome greatly exceed effects caused by transgene expression. Furthermore, we provide evidence that, (i) the impact of a low number of alleles on the global transcript and metabolite profile is stronger than transgene expression and that, more specifically, (ii) breeding for better adaptation and higher yields has coordinately selected for improved resistance to background levels of root and leaf diseases, and this selection appears to have an extensive effect on substantial equivalence in the field during latent pathogen challenge." (Kogel et al., 2010)

In another recent paper, dealing with biosynthetic comparison between tubers and leafes of potato traits (Ferreira et al., 2010), the authors come again to similar conclusions, as expressed in an interview of GMOSafety of the senior author³ in <http://www.gmo-safety.eu/en/news/741.docu.html> : "The impact of transgenes is basically limited to their immediate function". And furtheron:

"GMO Safety: The following statement was deduced from your findings: Conventional breeding causes more changes in plants than the introduction of a single transgene. Can you make such a generalisation? After all, you only looked at barley. Have comparable studies been carried out on other genetically modified crops?

Uwe Sonnewald: As far as I know, this was the first time that both methods had been used in a simultaneous investigation. Researchers have studied either gene expression or plant substances in wheat, potatoes and maize and have come to very similar conclusions. The impact of transgenes is basically limited to their immediate function. For example, if I insert a gene for fructan biosynthesis in potatoes, it is hardly surprising that these potatoes then produce fructan and so differ in this way from their parent lines. But only negligible additional differences were found. I know of no instance where a more significant change in gene expression has been caused by a single transgene. However, great variability exists between individual varieties of all the crops mentioned and the obvious explanation for this is that often the breeding objective is to create resistance to external stress factors, and this involves a large number of genes."

Again the same conclusions are drawn by another comprehensive paper of a large international collective of authors (Barros et al., 2010):

"The aim of this study was to evaluate the use of four nontargeted analytical methodologies in the detection of unintended effects that could be derived during genetic manipulation of crops. Three profiling technologies were used to compare the transcriptome, proteome and metabolome of two transgenic maize lines with the respective control line. By comparing the profiles of the two transgenic lines grown in the same location over three growing seasons, we could determine the extent of environmental variation, while the comparison with the control maize line allowed the investigation of effects caused by a difference in genotype. The effect of growing conditions as an additional environmental effect was also evaluated by comparing the Bt-maize line with the control line from plants grown in three different locations in one growing season. The environment was shown to play an important effect in the protein, gene expression and metabolite levels of the maize samples tested where 5 proteins, 65 genes and 15 metabolites were found to be differentially expressed. A distinct separation between the three growing seasons was also found for all the samples grown in one location. Together, these environmental factors caused more variation in the different transcript / protein / metabolite profiles than the different genotypes." (Barros et al., 2010).

Figure 2b demonstrates no evident differences between GM – and non-GM maize:

³ See <http://www.gmo-safety.eu/en/news/741.docu.html>

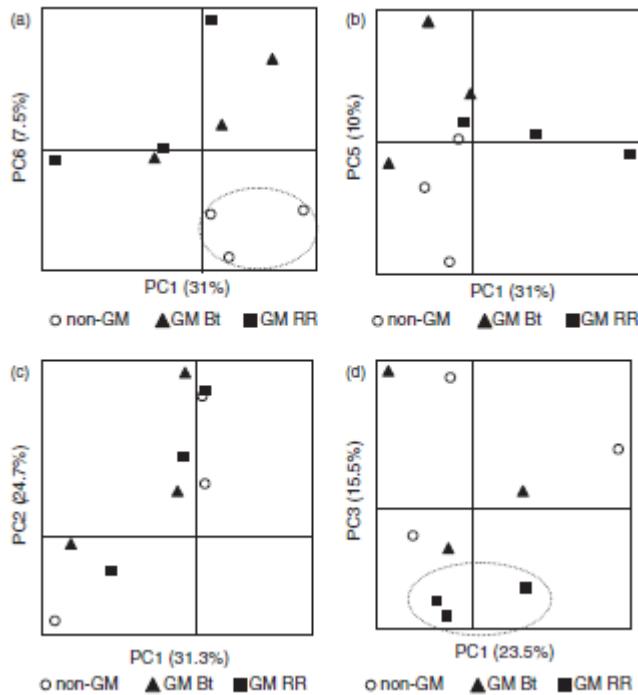


Fig. 3 PCA score plots of maize grown at Petit over three consecutive years. Separation between the non-GM and GM varieties for (a) microarray data, (b) proteomics data, (c) 1H-NMR spectra, (d) gas chromatographic/mass spectrometric (GC/MS) metabolite profiles. From (Barros et al., 2010).

Interestingly enough, the parallel short report on the website of USDA www.isb.vt.edu first was published under a misleading headline “Molecular Profiling Techniques Detect Unintended Effects in Genetically Engineered Maize”, it was subsequently corrected on intervention by the authors to the original headline given in the manuscript: “Molecular Profiling Techniques as Tools to Detect Potential Unintended Effects in Genetically Engineered Maize” (Barros, 2010).

It is also worthwhile to visit the site of David Tribe with GMO pundit, he offers an extensive site on genomic comparison between GMOs and non-GMOs, with an amazing collection of “natural transgenic plants”: <http://gmopundit2.blogspot.com/2005/12/collected-links-to-scientific.html>

One should also take into account, that many of the conventional breeding methods such as colchicination (Awoleye et al., 1994; Barnabás et al., 1999) and radiation mutation breeding (Reynolds et al., 2000) are obviously more damaging to the genome (Schouten & Jacobsen, 2007), and it is in addition not possible to clearly define what impact the un-targeted process could have caused. (Molnar et al., 2009) reported in detail about radiation treatment of the chromosome morphology of wheat hybrids: Dicentric chromosomes, fragments, and terminal translocations were most frequently induced by gamma-radiation, but centric fusions and internal exchanges were also more abundant in the treated plants than in the control amphiploids. The irradiated amphiploids formed fewer seeds than untreated plants, but on the other hand normal levels of fertility were recovered in their offspring. On the positive side the authors are confident that intergenomic translocations will facilitate the successful introgression of drought resistance and other alien traits in bred wheat. But it has to be admitted that

repair mechanisms on the DNA level are powerful (Baarends et al., 2001; Dong et al., 2002; Morikawa & Shirakawa, 2001). It is only logical that opposition within organic farming towards genetic engineering is now expanding also to some of those conventional breeding methods, some go even so far as to reject marker assisted breeding – typically for the organic agriculture scene, this trend is based on the myth of “intrinsic integrity of the genome”, for which term it is not possible in the literature to find a proper scientific definition based on comparisons (Ammann, 2008). The addition of rejected breeding methods would ultimately lead to an absurd situation, where most of the modern time traits would have to be rejected and breeding would be forced to start from scratch.

Basically, many of the first generation GM crops should be today subject to a professional debate on *deregulation*, and there is good and sturdy reason to state that many of these GM crops should not have been treated in such a special way in the first place, they can be compared in their risk potential to many crops created with traditional methods.

This should not be misunderstood as a plea for general deregulation of GM crops, rather for a strict and science based risk based regulation.

3.3. Regulatory dissent over molecular differences causes transatlantic divide

This actually includes a critical questioning about some basic rules of the United Nations Convention on Biological Diversity (CBD): transgenic crops of the first generation should not have been *generally* subjected to regulation purely based on the *process* of transgenesis alone; rather it would have been wiser to have a close look at the *products* in each case, as John Maddox already proposed in 1992 in an editorial in Nature (Anonymous, 1992). This is also the view of Canadian regulators (Andree, 2002; Berwald et al., 2006; Macdonald & Yarrow, 2002), where the *novelty* of the crop is the primary trigger for regulation. This transatlantic contrast has been commented by many (Bennett et al., 1986; Kalaitzandonakes et al., 2005; Ramjoue, 2007a, b; Snyder et al., 2008; Thro, 2004), and although for many years a solution and mediation seemed to be too difficult, contrasts can be overcome:

In a letter⁴ to the executives of the Convention on Biological Diversity (CBD), the Public Research and Regulation Initiative (PRRI) is asking for a scientific discussion in order to exempt a list of GM crops from the expensive regulatory process for approval, here only the final statement:

“Bearing in mind that the method of transformation itself is neutral, i.e. that there are no risks related to process of transformation, PRRI believes that there are several types of LMOs and traits for which - on the basis of the characteristics of the host plant, the functioning of the inserted genes and experience with the resulting GMO - it can be concluded that they are as safe as its conventional counterpart with respect to potential effects on the environment, taking also into account human health. ”

In a recent paper, an indiscriminate continuation of food biosafety research is questioned on the basis of all the above arguments by Herman et al. (Herman et al., 2009) with good reason:

“Compositional studies comparing transgenic crops with non-transgenic crops are almost universally required by governmental regulatory bodies to support the safety assessment of new transgenic crops. Here we discuss the assumptions that led to this requirement and lay out the theoretical and empirical evidence suggesting that such studies are no more necessary for evaluating the safety of transgenic crops than they are for traditionally bred crops.”

⁴ PRRI letter : http://www.pubresreg.org/index.php?option=com_docman&task=doc_download&gid=490

3.4. Perspectives for a dissolution of this divide

These new perspectives create hope, that solutions can be found:

In a first phase some of the widespread transgenic crops like transgenic maize with the Cry1Ab endotoxin should be exempt from regulation, which is indeed possible according to art. 7.4 in the Cartagena Protocol. In COP-MOP⁵ 2010 in Japan it should be possible, to amend the protocol with the introduction of a dynamics which allows to start the regulatory process with an initial phase focusing on the process of transgenesis, first following procedures proposed for non-target insects by (Raybould, 2010; Romeis et al., 2008), but in due time shifting later the focus on the product, making it possible to abbreviate the regulatory process wherever possible and feasible.

A conceptual framework is proposed by IFPRI/ISNAR in 2002, the International Service for National Agricultural Research (McLean et al., 2002), a careful evaluation of process-based versus product-based triggers in regulatory action can also lead to a merger of both seemingly so contrasting concepts into a legalized decision making process on which trigger should be chosen in a case by case strategy:

"Process-based triggers are the rule in almost all countries that have developed national biosafety regulatory systems; there are exceptions, however, where the novelty of the trait determines the extent of regulatory oversight and not the process by which the trait was introduced. While such a product-based approach to defining the object of regulation is truest to the scientific principle that biotechnology is not inherently more risky than other technologies that have a long and accepted history of application in agriculture and food production, it is less prescriptive than process-based regulatory systems."

Many of the debates on those two concepts suffer from a lack of clear-cut definitions, it will be important to have a close look at the Canadian regulatory system and the definition of PNTs (Plants with Novel Traits). In Canada, the trigger for risk-assessment is the *novelty* of the plant rather than the *methods* used to produce it. The difficulties start there, where a clear definition of PNTs is needed to come to a decision: It means that plants produced using recombinant DNA techniques, chemical mutagenesis, cell fusion, cis-genics or any other in-vitro technique leading to a novel trait, need to undergo risk assessment in the Canadian system. No wonder the Canadian definition of novel traits is rather wordy, but remains broad minded:

"A plant variety/genotype possessing characteristics that demonstrate neither familiarity nor substantial equivalence to those present in a distinct, stable population of a cultivated seed in Canada and that have been intentionally selected, created or introduced into a population of that species through a specific genetic change."

Conclusions:

There can be no doubt that product-based regulatory approaches are truest to the scientific principle that biotechnology is not inherently more risky than other technologies that have a long and accepted history of application in agriculture and food production, it is also less prescriptive than process-based systems, see McLean et al. (McLean et al., 2002).

⁵ Fifth meeting of the Conference of the Parties serving as the Meeting of the Parties to the Cartagena Protocol on Biosafety (COP-MOP 5), 11 – 15. 10. 2010 Nagoya, Japan <http://bch.cbd.int/protocol/meetings/>

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