

Are 'OMICS' Contributing to the Identification of Unintended Effects in Genetically Modified Crops?

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One of the initial concerns driving the risk assessment of genetically modified organisms (GMOs) in order to address their safety for human health and the environment has been the question whether techniques of genetic engineering and their molecular processes are inherently causing more unintended effects compared to those involved in traditional biotechnologies (e.g. breeding, chemical mutagenesis or radiation). In the context of genetically modified (GM) food and feed, a major guiding tool to address potential differences between the existing food/feed and the corresponding GM product is the concept of 'substantial equivalence' [1]. Based on the consideration that non-GM plants have a long history of safe use, genetically modified plants are compared to their non-genetically modified counterparts (parental or near-isogenic lines) in order to identify differences which are subsequently assessed for their impact on human health and the environment. With this approach, not only differences due to the acquisition of the new desired trait (intended by the genetic modification) are assessed, unintended changes (i.e. those which go beyond that of the original genetic modification such as altered expression of untargeted genes or metabolic effects of the novel gene product) are also considered.

The term "Omics" refers to studies involving different profiling techniques such as genomics (the quantitative study of genes, regulatory and non-coding sequences), transcriptomics (RNA and gene expression proteomics (protein expression) and metabolomics (metabolites and metabolic networks). Technical aspects in collecting 'omics' data set are continuously improving and profiling techniques now serve several distinct purposes. 'Omics' have for example the potential to provide complementary or additional tools to compare and study potential intended or unintended differences at the compositional and nutritional level between GMOs and their comparators (e.g. detecting differences in levels of nutrients, anti-nutrients, endogenous toxicants or allergens) or to characterize the GMO responses to environmental factors. Alongside with the progress in the area of 'omics' tools, the question has been raised whether there is a need for implementing molecular profiling techniques as a standard prerequisite in the risk assessment (environmental or food/feed assessment) of genetically modified organisms [2-5].

Over the last few years, several studies have been conducted to analyze the transcriptome profile of GMOs. For example, Coll et al. [6] have reported that the transcriptome profiles of commercial GM maize (MON810) and comparable non-GM maize varieties cultured in the field were very similar and that variability was greater between varieties of conventional lines. In another study investigating transcriptome alterations in both transgenic rice and rice lines obtained through chemical mutagenesis, Batista et al. [7] have shown that the acquisition of the traits is accompanied by modifications in transcript levels of untargeted stress-related genes in both lines. Moreover, the number of differentially expressed genes appeared to be larger in mutant lines compared to transgenic lines suggesting that crops with new traits obtained by 'traditional' mutation techniques are also prone to genetic alterations and/or rearrangements, which could lead to unintended effects.

While transcriptomics has the advantage to provide relatively reproducible data, differences revealed by transcriptome analysis may not be equally reflected in differences in the proteome and/or metabolome and as such in the plant's physiology. Therefore observations in alterations in a broad spectrum of metabolites could provide information that is complementary to the information obtained by transcriptomics or proteomics [8]. For example, metabolite profiling has been applied to compare several GM maize lines with their near-isogenic lines for several growing locations over several years [9]. From this study it was revealed that the impact of the environmental factors on the metabolomic profile was more pronounced than that of the genetic background. The applicability of the metabolite profiling approach has also been demonstrated to distinguish between changes induced by natural variability and by genetic modification in crops grown at different locations and/or growing seasons [10,11].

Implementing several profiling techniques in parallel to assess comparatively GM crops and their natural cultivars may offer a more holistic approach. For example, transcript profiling, metabolome profiling and metabolic fingerprinting have been used in parallel in order to assess the effects of transgene expression in transgenic barley relative to the influence of genetic background and the effect of plant interaction with mycorrhizal fungi [12]. Principle component analysis of the differentially regulated genes (microarray data) and metabolite profiling indicated that, in contrast to the transcriptome, alterations in metabolites were observed. The results also pointed to a higher impact of environmental factors (mycorrhization) in terms of metabolite differences compared to the effect of the introduction of transgenes or the effect of introgression of genes by classical breeding techniques. The conclusion that environmental factors cause more variation in the transcript / protein / metabolite profiles than the different genotypes has also been suggested by another study where transgenic maize lines were compared with the respective control line [13].

Out of the above-mentioned studies it appears that profiling techniques may provide new information for the safety assessment of GMOs by offering a holistic comparative approach relying on a broad screening, in a non-selective and unbiased manner. However, apart from the considerations on the costs of these approaches, the abundance of information generated could also raise challenges as regards the extraction of information with discernable biological

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meaning. From several studies, including those performed on organisms obtained through traditional plant breeding techniques, it becomes clear that transcriptional, proteomic and metabolite alterations may have different causes, including environmental and agronomical factors. Therefore, observed differences between GM plants and their comparators should be assessed for their relevance to the safety assessment in light of the natural plant variability, encompassing variability associated with genetic background (e.g. commercial available cultivars) and environmental impacts. This assessment is currently made difficult due to the lack of knowledge and information on the natural variation within and between given plant cultivars. For comparative purposes and in order to discern the bandwidth of natural plant variation under selected circumstances, it would be interesting to establish a database with a sufficient amount of samples, to develop standardized methods and to perform multivariate modeling of data [9,13]. In addition, some of the above-mentioned studies show that unintended changes may also occur with organisms obtained by traditional biotechnologies (such as breeding, chemical mutagenesis or radiation). Hence, it could be questioned on which basis genetically modified organisms obtained via transgenesis should be prioritized over those obtained by conventional breeding to identify, detect and assess potential adverse effects.

Last but not least, despite the continuous improvement in robustness and reproducibility of profiling techniques, the lack of homogeneity in experimental design and methodology is another factor that could hamper the development of feasible, large-scale methods that can be internationally certified and accepted. However, though standardization and validation of profiling techniques would facilitate the evaluation of the generated data on a routine basis within the context of comparative risk assessment of GMOs, it should be noticed that internationally agreed and certified standard procedures are also lacking for other types of experiments that are currently included in the biosafety dossiers of GMOs and that contribute to the overall risk assessment of GMOs.

Recent publication of several "omics" studies has shown the potential benefits and limits of the use of 'omics' tools in relation to the safety assessment of GMOs. Risk assessors should be aware of these developments and their possible application, including for risk assessment of plants that contain several different transgenes ('stacked events'), for GMOs of the second generation (such as plants that are intentionally designed to be physiologic or nutritionally significantly different), or for GM animals or micro-organisms.

Ideally, in order to optimize the beneficial use of profiling techniques in the risk assessment (and more particularly the hazard identification) of GMOs, it will be crucial to tackle the potential gaps of data and to identify the appropriate questions, in other words to distinguish what is 'nice to know' from what is 'need to know'. This approach would allow addressing the possible added-value of gathering molecular 'profiling techniques' data on a case-by-case basis and to take benefit of the progress in 'omics' technologies.

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