Comparative risk assessment and substantial equivalence

Existing EU regulations such as Regulations 178/2002 and 1829/2003 as well as Directive 2001/18 foresee a high level of protection for consumers and the environment. For example, in Recital 9 of Regulation 1829/2003 it says:

“This, genetically modified food and feed should only be authorised for placing on the Community market after a scientific evaluation of the highest possible standard, to be undertaken under the responsibility of the European Food Safety Authority (Authority), of any risks which they present for human and animal health and, as the case may be, for the environment.”

According to Regulation 1829/2003 (Article 4), it must be excluded that food and feed derived from genetically engineered plants has adverse effects on human health and the environment:

“(1) Food (…) must not:

(a) have adverse effects on human health, animal health or the environment;

(3) No GMO for food use or food referred to in Article 3(1) shall be authorised unless the applicant for such authorisation has adequately and sufficiently demonstrated that it satisfies the requirements of paragraph 1 of this Article.”

These regulations pose a huge challenge for the risk assessor. As already mentioned, the use of food plants is not restricted to specific purposes as it is with pharmaceuticals or pesticides. Rather, there are all kinds of uses and possible impacts on health and the environment that have to be considered together with agriculture and food production. Regardless of where these plants are grown or in which food and feed they might be used, the plants must be proven to have no adverse effects on health or the environment. For each relevant area of concern, specific and robust methods need to be developed together with assessment criteria. The following diagram gives an overview of some of the relevant topics.
In the toxicological assessment of single isolated compounds, it is very often possible to develop a solid hypotheses for targeted investigations, but this is much more difficult in the context of genetically engineered plants. In the risk assessment of genetically engineered organisms we are not dealing with clearly defined compounds, but with thousands of components that can show large variations in their composition. Consequently, the risk assessment of genetically engineered plants has to start with the uncertainties, and cannot at this point be narrowed down to well-defined potential hazards or be reduced to very specific risks. From a scientific point of view, this is a much bigger challenge than the assessment of chemically well-defined single substances.

The EU risk assessment tries to overcome this problem with a so-called “comparative approach”: Genetically engineered plants are grown side by side in experimental field trials. A comparison is made of some plant characteristics (such as height, yield and flowering) and the composition of several plant components. Although at first sight this may appear to be a reasonable approach, current practice does not allow sufficiently reliable conclusions. Some of the deficiencies are:

1. The very limited number of field sites (mostly below ten) and the short duration of the field trials (very often only one season) that do not allow reliable conclusions to be drawn on the risks of large-scale cultivation. In fact, these trials are nothing but a “snapshot” and certainly cannot reflect the whole picture. Once these plants have been granted authorisation for commercial cultivation, they will be grown under very different environmental conditions, where the opportunities for them to interact with the environment are very much increased. Moreover, their traits will be introgressed into other varieties that have a different genetic backgrounds. This can cause further unpredictable interaction between the genomes of the plants and the newly introduced genes. What is missing are comprehensive data on the interactions with the environment and biotic or abiotic stressors, including those varieties that are actually cultivated in the field.

2. The components used for comparison such as carbohydrates, amino acids and fatty acids and minerals, represent only a small percentage of relevant plant ingredients and their metabolic processes. For example, omics-data are not requested and neither is data on biologically active substances such as chemical transmitters or biological messengers such as miRNA. The problem arising from selecting of data that is too narrow is also relevant for the plant characteristics. For example, secondary seed dormancy, resistance to (non-target) pest organisms or reactions to more extreme climate conditions are not generated in a systematic manner. Furthermore, in many cases, it is not the whole plant that is investigated but only specific parts of it such as the kernels. Most data on plant components only concern the harvest, there are not many data on the different stages of vegetation. Consequently, relevant changes in plant characteristics and components can easily be missed.
3. Nearly all data show significant unintended changes in comparison to the plants’ composition. However, the biological relevance of these differences very often remains a matter of uncertainty. In most cases, these differences are not investigated further but are assumed to be irrelevant at the early stage of the investigations. Without generating further more specific data on the real range of variations under defined environmental conditions, such assumptions are not sufficiently reliable.

4. In parallel to the conventional plants that were used to create the genetically engineered plants (which are its ‘comparators’), there are further varieties used in the field trials as further ‘references’. These additional plants can show a large range of compositional differences, which are not relevant for the risk assessment. Data stemming from these reference plants can hide relevant differences between the genetically engineered plants and their true comparators. In fact, data from these reference plants are used by EFSA to justify not carrying out further investigations.

5. Some crucial data are not requested at all. For example, in trials with so-called stacked events (which are derived from crossings of genetically engineered plants), the parental plants are not requested to be grown in parallel. While EFSA, in its first guidance, previously requested such data (EFSA, 2007) these requirements were abandoned without sufficient justification in the following years.

6. All data from field trials are generated by industry without any independent control.

In recent years, some progress has been made as, for instance, a more detailed statistical analysis is now requested. Furthermore, data in the so-called ILSI database (see Then & Bauer-Panskus, 2010) can no longer be used for the purpose of specific comparisons. But nevertheless, this has not solved the general problems with comparative risk assessment. The deficiencies as described have a huge impact: Nearly all further steps in risk assessment carried out by EFSA are dependent on the outcome of the first comparison. If no evidence is found for potential hazards in this first step, then more specific investigations such as in-vitro tests or feeding studies with the plant or any long term investigations are not requested. Also in the opinion of EFSA, there is a substantial difference between the “comparative risk assessment” and a “comprehensive risk assessment” (EFSA 2011). Indeed, the comparative risk assessment is not much more than a cursory check and certainly nothing like a comprehensive, robust and reliable risk assessment.

Industry had considerable influence in setting the standards for comparative risk assessment. Especially relevant in this context is the International Life Sciences Institute (ILSI), an institution funded by food and agrochemical companies (see Then & Bauer-Panskus, 2010). Consequently, current EFSA practice is not in line with the requirements of the EU regulations: According to EU Regulation 1829/2003, the risk assessment has to be substantially different from an approach known as “substantial equivalence” that is applied in the US. This concept assumes that plants derived from conventional breeding can, in general, be regarded as substantially equivalent in comparison to genetically engineered plants, and only specific traits have to be taken into account for risk assessment. Until 2003, the concept of substantial equivalence, which is not sufficiently based on science, was also applied in the EU (Regulation 258/97), but was abandoned with the adoption of Regulation 1829/2003. As stated in the Regulation 1829/2003, Recital 6:

"Regulation (EC) No 258/97 also provides for a notification procedure for novel foods which are substantially equivalent to existing foods. 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. (...) this notification procedure should be abandoned in respect of genetically modified foods."

But according to the experts who developed the comparative approach for EFSA, the concept of substantial equivalence remained unchanged (Kok & Kuiper, 2003):

Although the Principle of Substantial Equivalence has received comments from all types of stakeholders (producers, regulators, consumers, evaluators, etc.), the basic idea behind the principle remains untouched. When evaluating a new or GM crop variety, comparison with available data on the nearest comparator, as well as with similar varieties on the market, should form the initial part of the assessment procedure. “

Indeed, the comparison of data as described above, is not only the starting point of risk assessment as performed by EFSA, but is in most cases also the end point. It is mostly based on insufficient data, but still the authority fails to request any further more specific toxicological investigations. As a consequence, EFSA is applying the ‘comparative approach’ as if the concept of ‘substantial equivalence’ were still be in place. In doing so, the authority is in conflict with the legal requirements of the EU.
Figure 2: Schematic overview of EFSA health risk assessment of genetically engineered plants, applying the so-called comparative approach.

In contrast, the EU Commission with its Implementation Regulation (503/2013) has substantially widened the remit of EFSA. For the first time, the request for 90-day feeding trials has become mandatory. However, the adequacy of such sub-chronic feeding trials that were developed for the testing of defined chemicals compounds is open to dispute. Furthermore, there can be no justification (as given in the Implementation Regulation) for exempting so-called stacked events, which can inherit very complex interactions emerging from the crossing of genetically engineered plants. But in regard to the overall authorisation process, these feeding trials as requested by the Commission do make a significant difference: It makes clear that – independently of the outcome of the first comparative step of risk assessment - further investigations are necessary.

Literature


