Advancing the Understanding of Biosafety

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Lecture

GM Maize and Glyphosate-Based Herbicides - Health Studies

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Session

Risk Assessment

An Appraisal of Current Approaches

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Introduction and context

The debate on the safety of genetically modified organisms (GMOs) used for food and feed is still very lively throughout the world, more than 15 years after their commercial release. Unfortunately although some stakeholders pretend there is a history of safe use of GMOs, there are no human or animal epidemiological studies to support such a claim, in particular because of the lack of labeling or traceability in GMO-producing countries. As a matter of fact, 97% of edible GMOs among cultivated ones (soy, corn and oilseed rape or canola, excluding cotton) are grown in South and North America. All these plants have been modified to tolerate and/or produce one or more pesticides, and thus contain their residues at various levels. These are mostly from Roundup, a major herbicide used worldwide and tolerated by around 80% of GMOs, or from modified Bt insecticide toxins directly synthesized by the GM plants from the transgenes. In fact, to analyze subchronic or chronic toxicological signs, it is more informative to concentrate on studies that include numerous blood and organ parameters. Most of these are 90 day-long feeding regulatory trials on rats eating GM corn or soy. It is the raw data of the companies which attracted our interest to this case; the raw data which we obtained by court order with the help of lawyers (since the data were kept confidential). We re-analysed these data and detected significant statistical differences (~9%) which concentrated mainly on kidneys and livers. These significant effects were all interpreted as non-relevant for the safety of GMOs by the companies as well as by the official competent authorities granting approval (e.g. EFSA). While the requirement for longer and more detailed regulatory tests would change the profitability of GMOs, they would protect mammalian and human health, which seems essential to us.

Debate on insufficiencies in the experimental design

All 90-day regulatory rat feeding studies with GMOs have been constructed according to the same scheme. The insufficiencies of the experimental design can be underlined as follows:

a) Too small a number of animals studied: Ten individuals measured for biochemical parameters out of 20 per group. This might be enough for long-term experiments, but not for such a short period of time. A small number of effects or of low amplitude are induced, similar to when a chronic pathology is slowly developing. These kinds of protocols could result in low power of statistical tests and therefore lead to many false negative results (for example to wrongly reject a possible effect of the consumption of GMOs). In such conditions, the observed effects would hardly constitute a sufficiently coherent and consistent clinical picture for the authorities to worry about.

b) Too many control rats: Additionally, the number of controls was four times higher in these regulatory tests, which have been used all over the world to authorize the main GMOs. Such an imbalance between control and treated rats conceals observable effects. This principle was accepted by official committees: out of 400 rats there were only 80 eating GMOs (and only 40 biochemically analyzed), thus four groups of ten animals, with two dosages (11 and 33 percent GMO in equilibrated diet), and two types of blood analyses per group (after five and 14 weeks).

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c) Too many control treatments: The 320 non-GM fed animals were treated in fact with seven different diets which were supposed to represent a variability of the possible regimen. Six constituted the so-called “reference” groups with feed not demonstrated as substantially equivalent. Moreover, two dosages in the control groups were chemically equivalent to the GM diets; they were made with the isogenic maize or maize close to the GM variety.

d) The rat was the only mammal fed with GMOs for three months.

e) The regulatory test was only performed once for each GMO, which was then supposed to be eaten all over the world.

f) The duration of 90 days is the longest test in the file and only on young adult mammals; it was not long enough to observe chronic effects.

g) The lack of developmental, reproductive as well as chronic or multi-generational tests is the subject of a heated debate for GMOs already commercially available.

This experimental protocol from Monsanto has been uncritically accepted by many competent authorities in the world, mostly confidentially. We deeply disagree with this design. Moreover, we underline the preoccupying side effects on liver and kidney physiology in particular, because they are the major detoxifying organs reacting in case of food intoxication.

Divergent biological interpretations

The biological interpretations become crucial after global statistical agreement, to some extent. Two possible issues arise here: either a demonstration of innocuousness (Monsanto et al.’s opinion), or preoccupying disruptions that should be followed by longer term tests prior to market approvals (our opinion). The main differences between Monsanto’s biological conclusions and ours, following statistical differences in biochemical and organ parameters, are these:

a) For the record, we would like to state that any early sign of difference should be collected in a table to get a global picture of the animal physiology after GMO consumption. It is really impossible within 90 days, with one single experiment in the world and such a small number of rats, to get a consistent toxicological picture. This is a major point because we are concerned about possible chronic pathologies. Some effects may not be of major amplitude yet; however, some are. For instance, the increase of the hearts' weight of 11 percent in males for NK603, or 40 percent increase in plasmatic triglycerides in females eating MON 863 (together with a pre-diabetic profile), could be considered as enough to trigger a moratorium. As a matter of fact, Monsanto did not repeat their studies.

b) The statistical differences are often compared to the GM-treated groups and the so-called “historical standards of the species” which are undefined, like the also undefined “normal range”. This allows one to simply consider larger variations as normal for subjective reasons. The differences have to be considered first with the closest control group, the isogenic control line. It is only afterwards that it could become possible to compare them with experimental reference groups (Monsanto et al. did that first) receiving a non-equivalent regimen (for instance at the level of salts or sugars). We recall that the reference groups are still too numerous in comparison to treated rats.

c) The significant effects are taken into account by Monsanto et al. only if they are similar in both sexes. This is denial of common scientific knowledge. The chronic pathologies, as well as the endocrine disturbances or some cancers, are usually sex-related and not proportional to the carcinogen dose taken over a short duration.

d) For Monsanto et al., the absence of dose-dependent effects is a reason to neglect the significant differences. This is absolutely unacceptable, just because, for instance, we need

to take into account endocrine disrupting antagonist possible actions. It has to be underlined moreover that this dose-dependency cannot be approached with a two-dose study as presented to the authorities by Monsanto (11 and 33 percent of GMO in the diet).

e) Since anatomo-pathological lesions could arise long after the beginning of a treatment or plasmatic biochemical disruptions, the necessity of correlations between these statistical differences and histopathological findings (overall within three months) cannot be requested to conclude on a preoccupying sign, by contrast to what is defended by Monsanto et al. In addition, histological slides and embedded organs are the property of the company, and were not double-checked by official committees or independent authors. We ask for an official counter-analysis, particularly of the male kidneys in these studies, which were found to concentrate more than 43 percent of all disrupted parameters, in a meta-analysis of all published data on commercialized GMOs. We already know that during the MON 863 study, Monsanto highlighted anatomic signs of “chronic progressive nephropathy” on GM-fed male rats’ kidneys. However, Monsanto did not see these signs as being noteworthy due to the fact that, according to them, they were well known to occur in old Sprague-Dawley rats. But these rats were only five months old, and still quite young at the end of the experiment. These anatomo-pathological signs on kidneys were not noticed during the studies on MON 810 and NK603 maize. Yet the rats were the same age and from the same strain.

f) The chemical composition of the food/feed is an important indication. However all insecticide toxins/herbicide residues/unintended or unknown metabolites (due for instance to insertional mutagenesis or new metabolites) are not assessed; thus the substantial equivalence with non-GM products is not proof of innocuousness.

g) A bias for biological interpretations could also be seen in the fact that the regulatory toxicological tests are presented to authorities and commented on only by the companies developing industrial products. A proposal for independent studies from companies to encompass this problem has been made to the Council of European Ministers.

Conclusions and perspectives

As a conclusion, we call for the promotion of transparent, independent and reproducible health studies for new commercial products, the dissemination of which implies consequences on a large scale. Lifetime studies for laboratory animals consuming GMOs must be performed, which would be in contrast to what is done today, like the two-year long tests on rats for some pesticides or drugs. These tests could be associated with transgenerational, reproductive or endocrine research studies. Shortcomings in experimental designs may raise major questions on other chemical authorizations.

Literature

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