Breckling, B. & Verhoeven, R. (2010) Implications of GM-Crop Cultivation at Large Spatial Scales.
Theorie in der Ökologie 16. Frankfurt, Peter Lang.

Roundup® in genetically modified plants: Regulation and toxicity in mammals[1]

Robin Mesnage, Emilie Clair & Gilles-Eric Séralini
(University of Caen, Institute of Biology, CRIIGEN and Risk Pole CNRS, Caen Cedex France. – criigen@unicaen.fr)

Context

Among the 134 million hectares of genetically modified plants growing worldwide in 2009, more than 99.9 % are described as pesticide plants (Clive 2009). Around 80 % are tolerant to Roundup, a glyphosate based herbicide. Its use on GMOs is thus amplified, and this phenomenon shed a new light on the problem of herbicide residues in plants. This is because these GM plants have been modified so that they can contain high levels of Roundup. They are modified to behave normally after several treatments with this herbicide, which were not allowed at such levels on regular plants before. The latest generation, like Smartstax crops, even cumulate a tolerance up to 2 herbicides and a production of 6 insecticides. By this widespread use and the known potential hazards of pesticides, their residues are a major concern for health and the environment. Moreover the new metabolism that they could trigger in GMOs remains to be studied. A debate on international standards is ongoing on their capacity to predict and avoid adverse effects of the herbicide residues at environmental or nutritional exposures, particularly in GMOs.

As far as Roundup is concerned, the formulations of which are mixtures of only one proposed active ingredient (glyphosate) with various adjuvants, up to 400 ppm of residues are authorized in some Genetically Modified food and feed (EPA 2008). It is also recognized by regulatory agencies that these residues are found in meat and products generated from livestock fed with glyphosate tolerant soya or maize (EFSA 2009).

Review on Roundup toxicity studies

Surprisingly, more and more studies have revealed unexpected effects of Roundup, including carcinogenic and endocrine disrupting effects. This is at lower doses than those authorized for residues found in Genetically Modified Organisms (GMOs). For example, Roundup altered the spermatogenesis of rats exposed in utero to 50 ppm per day (Dallegrave et al. 2007). Even a tumour promoting potential is observed on mice

1 Extended abstract: A full paper is submitted to UWSF – Zeitschrift für Umweltchemie und Ökotoxikologie, Series: Implications of GMO-cultivation and monitoring. Springer-Verlag.

exposed to 25 ppm per day (George et al. 2010). Alterations of rat testicular morphology and testosterone levels occur at doses of 5 ppm per day (Romano et al. 2009). In our laboratory we have observed endocrine disruption on human cell lines; it was a disruption of aromatase, of the androgen and estrogen receptors in 24 hours, starting from 0.5 ppm Roundup. This corresponds to glyphosate concentrations 2000 times less than the authorized levels in GMOs (Gasnier et al. 2009). Furthermore, we have shown that Roundup inhibited cellular respiration, and that it also caused membrane damages. Last but not least, Roundup showed genotoxic effects, as well as it induced apoptosis and necrosis in human cells (Benachour & Séralini 2009). Most of these effects are amplified with time. This is preoccupying, and it does highlight the limits of the Acceptable Daily Intake concept for long term exposures.

Debate on health risks

In all these studies, toxic effects were not detected with the so-called active ingredient glyphosate alone at these doses; they were more related to the formulations of the herbicide and its adjuvants. These remain confidential and their residues are not measured. Out of the 20 tests required (or conditionally required) to register a pesticide in the United States, only 7 short-term acute toxicity tests use the whole formulation; the others are done using the sole active ingredient (Cox & Surgan 2006). The problem of pesticide registration is indeed very old, and it is only the active ingredient that is tested in chronic mammalian toxicity tests (generally for 2 years on rats). Moreover there is generally only one 2-year test worldwide on a mammal per pesticide, performed by the company commercializing this pesticide. Adjuvants are often considered to be inert in the assessment process. This is a major issue. Such a simplistic approach of pesticides hazards bypasses the potential effects of adjuvants and their mixtures with the active ingredient on chronic risks. This issue is even more crucial with GMOs which are designed to tolerate the formulations that enter the edible plant cells.

Nevertheless, it is well known that adjuvants are mixed with the active ingredient in order to increase the efficiency of formulations. In medicine, adjuvants are also used to increase the molecule absorptions, or the effectiveness of vaccines. In chemical products such as pesticides, they are used to increase targeted toxicity (for example penetration in leaves or insects), but they do have an effect also on non specific targets too. Some known adjuvants of Roundup such as polyethoxylated tallowamine (or POEA) showed more toxic effects than glyphosate in various models, and even more than Roundup in some cases on aquatic life for example (Tsui & Chu 2003; Marc et al. 2005) or on human cells (Benachour & Seralini 2009).

By only considering the active ingredient, regulatory thresholds seem to guarantee the safety of residues, however we conclude that it is not the case with the whole formulations, in particular those specific to GMOs. In conclusion, confidentiality on the composition of formulations must be lifted, as announced recently by the U.S. Environmental Protection Agency following our work (EPA 2009). People consuming GMOs are thus

exposed to residues of many formulations which are themselves mixtures of different chemicals. The long term combined effects have never been evaluated, not even in laboratory animals. We suggest that regulatory agencies change their paradigms and integrate modern knowledge, in order to guarantee the safety of pesticides residues, in particular when associated with genetically modified plants.

References

Benachour N., Seralini G.E. (2009) Glyphosate formulations induce apoptosis and necrosis in human umbilical, embryonic, and placental cells. Chem Res Toxicol 22: 97–105.

Clive J. (2009) Global Status of Commercialized Biotech/GM Crops: 2009. ISAAA Brief 41.

Cox C., Surgan M. (2006) Unidentified inert ingredients in pesticides: implications for human and environmental health. Environ Health Perspect 114: 1803–1806.

Dallegrave E., Mantese F.D., Oliveira R.T., Andrade A.J., Dalsenter P.R., Langeloh A. (2007) Pre- and postnatal toxicity of the commercial glyphosate formulation in Wistar rats. Arch Toxicol 81: 665–673.

EFSA (2009) Modification of the residue definition of glyphosate in genetically modified maize grain and soybeans, and in products of animal origin on request from the European Commission. EFSA Journal 7: 42.

EPA (2008) Federal Register / Rules and Regulation. 73588–73592.

EPA (2009) Glyphosate final work plan (FWP) Registration review case No. 0178.

Gasnier C., Dumont C., Benachour N., Clair E., Chagnon M.C., Seralini G.E. (2009) Glyphosate-based herbicides are toxic and endocrine disruptors in human cell lines. Toxicology 262: 184–191.

George J., Prasad S., Mahmood Z., Shukla Y. (2010) Studies on glyphosate-induced carcinogenicity in mouse skin: A proteomic approach. J Proteomics. 73: 951–965.

Marc J., Le Breton M., Cormier P., Morales J., Belle R., Mulner-Lorillon O. (2005) A glyphosate-based pesticide impinges on transcription. Toxicol Appl Pharmacol 203: 1–8.

Romano R.M., Romano M.A., Bernardi M.M., Furtado P.V., Oliveira C.A. (2009) Prepubertal exposure to commercial formulation of the herbicide glyphosate alters testosterone levels and testicular morphology. Arch Toxicol. DOI: 10.1007/s00204-009-0494-z.

Tsui M.T., Chu L.M. (2003) Aquatic toxicity of glyphosate-based formulations: comparison between different organisms and the effects of environmental factors. Chemosphere 52: 1189–1197.