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Testing Time for Substantial Equivalence: *Daphnia magna* survival and fitness reduced when fed MON810 (Bt Cry1Ab) maize

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Commercially, insect-resistant transgenic (GMO) plants are made by inserting a gene coding for one of a family of toxins produced by the soil bacterium *Bacillus thuringiensis*. These Bt toxins are regarded by most regulators to be safer for the environment than externally applied synthetic pesticides and this is because, as plant-expressed proteins, they are considered specifically targeted to organisms that consume the crop (Glaser and Matten, 2003). As a result of this understanding Bt toxins expressed by transgenics are managed as a 'public good' by the US Environmental Protection Agency (USEPA 1998).

However, Bt toxins are often expressed at high levels within plant tissues (typically for insertion event MON810 this is around 10ug/g fresh weight of Cry1Ab) and they persist in the soil, either within plant cells or as native protein (Baumgarte and Tebbe 2005; Griffiths *et al.* 2006). Therefore, contained within a field of Bt maize there can be many kilograms of a Bt protein at any one time. As a consequence, there is potential for significant exposure of non-target organisms, both in and around fields growing transgenic Bt crops.

Environmental risk assessments of transgenic crops have until now focused exclusively on consequences for non-aquatic organisms (NRC 2000). A recent study however, showed that debris and pollen of plants transgenic for Bt-toxins can enter nearby agricultural streams in large quantities (Rosi-Marshall *et al.* 2007). This same paper also reported that two caddisfly species, which are ecologically important stream organisms, are sensitive to Cry1Ab-containing leaves and pollen (Rosi-Marshall *et al*. 2007). As Bt researcher Angelika Hilbeck (ETH-Zurich) told the BSR News Service: "We have entirely overlooked aquatic ecosystem effects of transgenic toxins".

Now, a further aspect of freshwater toxicology has been addressed by a study published in the journal *Archives of Environmental Contamination and Toxicology*. This study reports that *Daphnia magna*, a freshwater crustacean arthropod commonly used in toxicological investigations, can also be negatively affected by Bt transgenic plant debris containing the Bt toxin Cry1Ab (Bøhn *et al*. 2008). In this study, *D. magna* populations were fed either kernels of ground transgenic maize (containing event MON810) or non-modified isogenic maize kernels. The plant material for these experiments was grown in adjacent fields.

The Results

Bøhn *et al*.'s findings were that mortality, growth and fertility of *D. magna* were all negatively affected by the MON810-containing line compared to the control maize. Interestingly, however, the animals fed transgenic maize showed early maturation, indicating a likely toxic response to a component of the transgenic maize, rather than

"The aim of science is not to open the door to wisdom but to set a limit to error."
Bertolt Brecht

a response to malnutrition.

The authors suggest that their results reinforce the possibility that Cry1Ab transgenics may have significant implications for aquatic ecosystems. However, the mechanism by which the transgenic maize affects *D. magna* is not resolved by this data. One possibility is that the assumption that Cry1Ab is lepidopteran-specific may be inaccurate or, alternatively, Cry1Ab may be modified within the cellular environment of plants. In either case, transgenic Cry1Ab, and perhaps other cultivars containing different Bt toxins, may be toxic to non-target organisms to an unexpected degree. Cry proteins may thus be having effects on soil arthropods (for which there are no published studies on Bt toxin effects). Angelika Hilbeck however is cautious: "It is difficult to make cross-comparisons from water to land ecosystems, since they are such different environments".

Since MON810 was the only Cry1Ab event studied by Bøhn *et al*., there remains an alternative mechanistic possibility however, which is that the effects on *D. magna* are a result of some unanticipated consequence of transgene insertion or expression. Such unanticipated effects are not merely theoretical: Rosi-Marshall *et al*. normalised their results for C:N ratios because Cry1Ab containing Bt maize varieties have more lignin than non-Bt varieties (Saxena and Stotzky 2001). This normalisation was done to prevent any confounding influences of nutritional quality from affecting their results (Rosi-Marshall *et al*. 2007).

A recent paper detailing the first proteomic analysis of a MON810-containing cultivar may be relevant to this discussion. The authors found at least 43 significant protein expression differences between the MON810 line and a near-isogenic control (Zolla *et al*. 2008). Given this perhaps surprising degree of difference between a transgenic cultivar and a non-transgenic isoline, it becomes plausible to imagine that one of these differences might be responsible for the effects observed on *D. magna*.

A substantial equivalence connection?

Irrespective of whether Cry1Ab (or some other MON810 constituent) turns out to be the specific cause of increased *D. magna* mortality, Bøhn *et al*.'s result (and also the caddisfly result) constitute a challenge also to the regulatory doctrine of substantial equivalence. According to this principle, MON810 has been declared 'substantially equivalent' and it should be safe for all organisms (other than known targets of Cry1Ab), whether they are *D. magna* or humans. Instead, MON810 is apparently substantially equivalent but not safe.

These new results may stimulate discussion of the concept of substantial equivalence and its relationship to GMO safety. One possible interpretation of this data is that it disproves absolutely the existence of any fundamental relationship between substantial equivalence and safety. Instead, it supports the view that substantial equivalence was never a true scientific concept, as has been argued, it is a regulatory 'principle' associated with no biological relationship nor any theoretical validity (Millstone *et al*. 1999).

Other interpretations are also possible however: that substantial equivalence is still useful, even if the relationship with safety is not absolute. In this view recent results weaken the relationship but do not disprove it, rather like examples of differences between human and rat toxicology weaken, but do not wholly invalidate, the predictive power of that relationship. In either event it may no longer be appropriate to say that a transgenic crop is substantially equivalent and therefore safe.

Thomas Bøhn however takes a very different tack: his answer to this conundrum is that MON810 was originally determined incorrectly by US (and also EU) regulators as

substantially equivalent. This answer however, illustrates another apparent problem of substantial equivalence: that there is no agreed, universal or *a priori* set of criteria of what, in terms of crop composition, constitutes a finding of a substantial difference (Millstone *et al*. 1999).

Other things being equal, substantial equivalence, it seems, will either have to be reconsidered, or it will acquire the probably unique distinction of violating *twice,* Karl Popper's falsifiability criteria of a scientific theory.

Put another way, is substantial equivalence so elastic, either in its specific determination for a particular crop, or in its application as a general measure of safety, that it is not in practice falsifiable?

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