A briefing document for non-specialists describing the lack of regulation of a new class of products and GM crops based on dsRNA technology

by
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This is a briefing about the contents of a new, peer-reviewed scientific paper: "A comparative evaluation of the regulation of GM crops or products containing dsRNA and suggested improvements to risk assessment" by Professor Jack Heinemann, Sarah Agapito-Tenfen and Adjunct Associate Professor Judy Carman.

To date, most[1] genetically modified (GM) plants have been made by inserting a new piece of DNA into a plant so that the GM version makes a new protein. Most of these new proteins are designed to either kill insects that try to eat the plant or to make the plant resistant to a herbicide. The process works like this: the DNA is changed so that when a section of the DNA is read and copied, a new piece of messenger RNA (mRNA) is made. The mRNA then goes to another part of the cell and is read to make the new protein.

However, there is a new type of GM plant now being made. These are not designed to make a new protein, but to just make a new RNA molecule. However, the RNA molecule made is different to the single-stranded mRNA described earlier, because it is either double-stranded (dsRNA) or it is designed to find another single-stranded RNA molecule and bind to it to create a dsRNA molecule. These dsRNA molecules have important roles in cells. For example, they can silence or activate genes. For this to happen, the order of the nucleotide units in the dsRNA molecule is crucial. A different sequence can result in the dsRNA having different effects, and silencing or activating a different gene, or multiple other genes.

A number of GM plants have now been made using this technology. For example, Australia's CSIRO has developed GM wheat and barley varieties where genes have been silenced in order to change the type of starch made by the plant. Another example is biopesticide plants, which are designed to silence a gene in insects that eat the plant. That is, the insect eats the plant, the dsRNA in the plant survives digestion in the insect, travels into the tissues of the insect to silence a gene in the insect so that the insect dies as a result.

There is evidence that the gene silencing may be inherited by the offspring of some organisms that eat the dsRNA.

Furthermore, there is massive, on-going investment occurring to develop products that directly transfer dsRNA into the living cells of plants, animals and microbes via their food or by being absorbed through their "skin". This allows dsRNA molecules to be sprayed onto fields of crops to kill insects or to be delivered to beehives as oral medicine for bees.

Last year, a high profile scientific paper was published that showed that dsRNA molecules produced in non-GM plants can be taken into the bodies of people who eat the plant. The dsRNA from the plant was found circulating in blood, indicating that it survives cooking and digestion. Research has also shown that:

- at least one dsRNA produced in plants (called mir168a) can change the expression of genes in mice; and
- dsRNA (mir168a) can change the expression of a gene in human cells growing in tissue culture.

Therefore, there is a real risk that the dsRNA produced by these new GM crops could survive digestion in

[1] There are some extremely minor exceptions to this, such as virus-resistant papaya, some nutritionally-altered soybeans, and some other plants that are not yet on the market.

people and change how those people's genes are expressed. These effects of dsRNA were predicted long ago by some scientists. The proof has now arrived.

So, are all dsRNA molecules safe?

A new paper has just been published in Environment International by Professor Jack Heinemann of New Zealand, Sarah Agapito-Tenfen of Brazil and Adjunct Associate Professor Judy Carman of Australia. These authors looked at how the safety of some plants, designed to produce new dsRNA, was determined. They reviewed their experience with three government safety regulators (for either food or the environment) in three different countries over the past ten years. They found that the safety of dsRNA molecules was usually not considered at all, and if it was considered in any way, the regulator simply **assumed** that any dsRNA molecules were safe, rather than **requiring proof** that they were safe.

The authors found that government regulators:

- dismissed any need for any assessment of the sequence of the nucleotides in the dsRNAs produced by GM plants;
- seemed to assume that dsRNAs produced by these plants are much the same as the more fragile single-stranded RNAs (eg mRNA), and therefore would not survive cooking and digestion; and
- claimed that these new dsRNA molecules are safe because humans and non-target animals would simply not be exposed to them.

However, the authors found many scientific studies showing that these assumptions were incorrect.

As a result, the regulators did not assess whether the dsRNAs could cause adverse effects in people or in the environment by, for example, silencing or activating genes in people that come into contact with the plant when it is grown commercially. Contact could include eating the crop or processed products derived from it, inhaling dust from the crop when harvesting it, or inhaling flour from the crop when baking with it. And regulators made that decision regardless of whether the dsRNA was generated intentionally or unintentionally by the crop. All three regulators decided that there were no risks to be considered, based on their own unproven and incorrect assumptions, rather than the scientific evidence.

As a result of their analysis, the authors developed and provided a safety testing procedure for all GM plants that may produce new dsRNA molecules, as well as for products where the active ingredient is dsRNA.

It is important to realise that our current understanding of dsRNA in GM plants is in its infancy and we are still trying to understand how dsRNA molecules may work and therefore how they may affect humans, animals and the environment. Even so, some GM plants using this technology have already been approved for human consumption, using the sorts of assumptions described earlier. Of these crops, several have been withdrawn from the market, while others are about to enter it.

Meanwhile, spraying dsRNAs directly onto crops can be expected to result in large exposures to dsRNA molecules in the environment. For example, we know that existing agricultural sprays can travel for several miles on the wind and can enter surface water and ground water due to run-off after rain. This will also happen with dsRNA molecules if they are sprayed onto crops. We also know that dsRNAs can persist for a long time in the environment.

GM plants and products based on dsRNA technology need a thorough, fit-for-purpose safety evaluation before we use them commercially. The authors provide a step-by-step procedure of how this could be done.

After all, we don't want to learn that one or more of these crops or sprays is toxic after millions of people have been exposed to them for years.