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INBI statement on FSANZ response to new research on safety testing GM foods with dsRNA molecules

FSANZ: proving us wrong is a win win (for both you and us)

Two months ago we published a thorough and rigorously peer-reviewed evaluation of the safety assessments conducted on a new kind of GM ingredient in food (Heinemann et al., 2013). That ingredient is called double-stranded RNA (dsRNA). Our work used the best available scientific research to conclude that dsRNAs in food or other products should be evaluated for safety using fit-for-purpose tests.

We were able to show that as evidence for this need accumulated over the last decade, some regulators including Food Standards Australia New Zealand (FSANZ) dismissed that evidence using assumptions rather than scientific testing. The evidence for the need for testing only continues to grow.

The response from FSANZ[1] to our research is unfortunately a denial that safety studies should be done.

When FSANZ says it is not "likely" that small dsRNAs in foods will harm humans, it effectively acknowledges this is still possible, and so a risk. Yet it proposes not even testing for that risk until the "weight of evidence" suggests it is doing harm. We say that there is sufficient evidence to do the tests: don't wait for harm to be proven.

Importantly, FSANZ only attempts to address oral exposures and fails to address inhalation or absorption through skin. These are relevant and different pathways that must be tested.

Moreover, the weight of evidence they rest upon is either not appropriate for the testing of new dsRNAs in food, or simply is an absence of evidence because of an absence of testing. FSANZ has the power in its legislation, it has the option under international food safety guidelines, and it has a responsibility to the people of Australia and New Zealand to ask for evidence of no detectable adverse effects from new dsRNAs in specific GMOs.

The purpose of risk assessment is to identify risk and then mitigate it before harm arises. FSANZ seems to be suggesting that they cannot ask for these risks to be investigated because they are awaiting scientific evidence that someone has already been harmed. We say: get the evidence of safety; don't wait for harm.

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[1] http://bit.ly/13DHSKQ

- FSANZ claims that we underestimate "the strengths of the GM food safety assessment to detect possible unintended effects" that may be caused by dsRNA. This is wrong.

  What we do know is that FSANZ does not require animal feeding studies of any kind. In the approvals that we reviewed, it had never even required tests for detecting dsRNA in the blood of animals, much less required tests that would reliably detect unintended harmful effects from dsRNA. FSANZ does not monitor for effects on people after approval or specify any particular monitoring be done by the developing companies. FSANZ needs to do more than just say its processes work; it needs to be forthcoming on what evidence it relies on to show that all these new dsRNA molecules are no threat to humans.

- FSANZ makes a number of factual errors and logical non-sequiturs in its response. For example, FSANZ says that there is no scientific basis for positing that novel dsRNAs in food would cause an effect on people.

  Contrary to what FSANZ asserts, there is scientific basis for suggesting that small dsRNAs present in some GM foods may pose a greater risk than those already naturally abundant in conventional foods. The effects of dsRNA in food are shown through the development of dsRNAs intended to be toxic to animals and are the basis of new pesticides. Animal toxicity is often used as evidence for potential toxicity to humans.

  If there were no scientific basis for assuming that novel dsRNAs could have profound effects on human beings, then why by FSANZ's own admission have there been so many attempts by the pharmaceutical industry to try and cause these effects? Surely these pharmaceutical researchers think it not just plausible, but probable and so do their stockholders.

  On this point, FSANZ also cites evidence of a physiological effect of a drug based on dsRNA applied to skin. Food, in the form of flour or liquids, also touches human skin and can be breathed in, leading to inhalation exposure. FSANZ never addresses these risk pathways.

  Furthermore, because drug developers may frequently fail does not mean nature will fail to deliver a potentially harmful dsRNA present in food. People also failed initially to build flying machines based on flapping bird wings. But birds nevertheless still managed to fly. And eventually airplanes were invented.

- FSANZ says that we failed to account for natural dsRNA already in food. This is wrong.

  RNA molecules are in the food we eat, but to extrapolate from the safe use of food with naturally occurring forms to those that are engineered and unique to new kinds of food is wrong. Proteins of all kinds are also in the food we eat but new proteins are evaluated for the potential to be toxic or allergenic in food. These dsRNA molecules can participate in fundamental biological reactions in human cells and so must be tested to be determined safe.

- FSANZ claims that we rely on only one paper. This is wrong.

> Our research was split into "food safety assessment" and "environmental safety assessment" because these are often done differently, respond to different sources of international guidance and oversight, and by different regulators. Only part of our paper was therefore on food. We drew on many different sources to evaluate the evidence that dsRNAs may be taken up by humans through food (orally, breathed in, absorbed). Two recent papers, one from an academic research laboratory and the other from Monsanto, which has commercial interests in dsRNA, both confirm detecting dsRNAs of plant origin in mammals(Zhang et al., 2012b) and both mammals and people (Zhang et al., 2012a).
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> Combined, these papers confirm that dsRNAs can be taken up through food. The paper by Monsanto attempts to argue that many prior detections may be due to contamination, but it never shows that to be the case except in its own studies. Moreover, it never refutes the study by the academic laboratory. We discuss this at length in our research but unfortunately FSANZ seems to have overlooked this discussion.

FSANZ has mis-mashed disparate studies of different kinds, with different endpoints, unrelated testing approaches and which use different kinds of delivery to produce doubt about whether safety testing is needed. Invoking a series of failures to cause a physiological effect in people using different kinds of dsRNAs found naturally in food or which were generated in laboratories for other purposes is a broad stroke approach to risk assessment that is inappropriate for concluding the safety of new dsRNAs in food.

Meanwhile, it has not offered empirical evidence of safety. This is neither true to case-by-case risk assessment nor is it substantial reassurance that new dsRNAs are safe in the food products that FSANZ has approved.

In contrast, what we have shown in our research is that FSANZ has made a series of historical assumptions that in retrospect have proven incorrect. These assumptions were not its only choices because not everyone made them even at that time. Thus FSANZ could have made other choices then and now.

We acknowledge that there exist different scientific opinions on how to conduct risk assessments on GM foods and on other products that might contain novel dsRNAs. We anticipate that over time our recommendations will be improved upon. This will be the outcome of implementing actual testing and advancements in science.

However, at this time there is almost no experience with novel dsRNAs in food or other products and no monitoring of effects in the people who have eaten them. There has been little or no specific testing data published in the peer-reviewed literature coming from studies that would be designed to demonstrate the safety of novel dsRNAs on a case-by-case basis. In our research, we found no such specific testing in the cases we examined, including those that got FSANZ approval. The science exists to do the testing; it just hasn't been required.

It makes sense to agree to what tests are appropriate, and to conduct them while such products are rare rather than wait until dsRNAs are in many consumer products.

Given all this, we suggest that it would be much more credible for FSANZ to restart this conversation from the vantage point of having experience with actual testing of novel dsRNAs on a case-by-case basis, and then move later to a discussion of whether more or fewer tests are warranted.

Let's use scientific evidence to assure that the new dsRNAs in these foods are safe and prove us wrong about the need to test. We would love to be proved wrong.

Heinemann, J. A., Agapito-Tenfen, S. Z. and Carman, J. A. (2013). A comparative evaluation of the regulation of GM crops or products containing dsRNA and suggested improvements to risk assessments. Environ Int *55*, 43-55.

Zhang, L., Hou, D., Chen, X., Li, D., Zhu, L., Zhang, Y., Li, J., Bian, Z., Liang, X., Cai, X. *et al.* (2012a). Exogenous plant MIR168a specifically targets mammalian LDLRAP1: evidence of cross-kingdom regulation by microRNA. Cell Res *22*, 107-126.

Zhang, Y., Wiggins, E., Lawrence, C., Petrick, J., Ivashuta, S. and Heck, G. (2012b). Analysis of plant-derived miRNAs in animal small RNA datasets. BMC Genomics *13*.