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‘Safety assessments of GMOs are non-existent’

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US-based systems biologist Shiva Ayyadurai created a controversy recently by claiming that his studies had found that genetically modified soya bean plants had less capacity to get rid of toxins such as formaldehyde compared to non-GM counterparts. The idea that GM technology disrupts a plant’s natural metabolism was seized upon as vindication by anti-GM activists even as it came under criticism from others. In a wide-ranging interview, *BusinessLine* spoke via conference call to Shiva Ayyadurai, whose current research focuses on developing systems biology methods to understand bio-molecular phenomena, and three other scientists who make a strong pitch for increased regulation and transparency in GM foods — Michael Hansen, senior scientist at the non-profit Consumer Union working on consumer-related policy issues; Ray Seidler, a former senior scientist at the US Environmental Protection Agency (EPA); and Hema Yadav, an agricultural expert who has worked on capacity-building for farmers and managers in India and Africa. Excerpts:

In a nutshell, the essence of your hypothesis seems to be: Like all plants, genetically modified soya bean produces formaldehyde, a carcinogen; but unlike non-GM soya bean, it depletes glutathione, a key anti-oxidant that helps plants remove formaldehyde and other toxins from their cells. As a result, it is wrong to suggest that GM soy is equivalent to non-GM soy and, by implication, that GM plants are equivalent to non-GM plants. Does this make for a fair description?

Shiva Ayyadurai: Yes, our systems analysis shows that GM soy is substantially different from non-GM soy. The critical point is that we used a systems biology approach — the first of its kind — to look at a critical molecular system called C1 Metabolism, which occurs in all plants, bacteria and fungi. In that molecular system, there are three sub-systems: methionine biosynthesis, methylation and formaldehyde detoxification. The goal of this systems approach was to explore if GM plants are the same as, or “substantially equivalent” to non-GM plants. We based the study on integrating molecular pathway information from 6,497 wet lab experiments done in 184 institutions, across 23 countries, on what occurs from genetic engineering to produce Roundup Ready Soy (RRS), the GM soy, and whether such GM causes disruption to C1 Metabolism. We found that there is a significant disruption, particularly to formaldehyde detoxification, following insertion of the foreign gene.

Our analysis concludes that, in GM soy, oxidative stress is caused by the GM, resulting in glutathione, a natural anti-oxidant, being depleted and formaldehyde accumulating. Formaldehyde does exist in all plants, at various levels, and detoxification occurs at different stages. However, in the GM soy, since the formaldehyde detoxification pathway is perturbed, this analysis shows that the levels of formaldehyde and glutathione will vary between GM soy and non-GM soy.

Your research did not involve testing actual plants. So why rely wholly on a ‘systems biology’ approach? Why didn’t you bother to validate this by testing a few transgenic and non-transgenic varieties of soy? Wouldn’t that have strengthened your hypothesis?

Michael Hansen: Clearly, such testing needs to be done and that will be in a forthcoming paper. By the way, this series of four papers is based on thousands of wet lab tests and is not “just a model”. This paper is focused on using modern systems biology methods to provide a foundation, at the molecular level, for all researchers to understand, with full transparency, how GM may perturb complex molecular systems. There is an active effort towards conducting wet lab tests on the results indicated from this systems biology analysis. However, conducting such experiments is

extremely difficult, given the lack of transparency from those who own, manufacture, and control those GM seeds, be it soy or others. For example, there are legal constraints in the US to even obtain the seeds to conduct such testing.

Ayyadurai: The systems biology approach is the most important contribution of this series of four papers, and aims to advance the scientific method in a far more transparent and integrative manner to get an accurate view of what is going on in GM versus non-GM. Today, scientists primarily do individual, single experiments using the scientific method, where they first begin with a hypothesis, then do a single experiment, and then gather and organise the data from that experiment. The data is then analysed to build a model, which makes a prediction. The predictions are published, which motivates others to do more experiments, and this cycle of the scientific method is repeated to generate more data and new predictions, until there is consensus on the predictions.

The biggest breakthrough in biology took place after the human genome project ended in 2003, where biologists realised that humans have the same number of genes as a worm, motivating biologists to recognise that the complexity of an organism is not a function of the number of genes, but can only be understood by interconnecting the complexity of molecular pathways derived from multiple experiments, and recognising the need to interconnect molecular pathway information, so we move away from what is called reductionist biology to a systems biology. Reductionist biologists are like guys looking at pieces of an elephant (just the trunk, the ears, tusk, and so on) and each making assumptions on what they think it is, leading them often to erroneous and biased conclusions. Systems biologists attempt to look at the connections across the whole organism, and put it all together to get a more accurate, unbiased view. So, that's what we did across the series of four papers, step-by-step:

Paper I: Aggregates over 11,000 papers to identify the fundamental molecular pathways of C1 Metabolism (published in *Agricultural Sciences*).

Paper II: Interconnects the molecular pathways of C1 Metabolism, in normal condition, using a systems approach. This paper shows that formaldehyde is detoxified, and glutathione is maintained in normal plants (published in *American Journal of Plant Sciences*).

Paper III: Identifies the molecular pathways of oxidative stress in plants, connects them and integrates them with the C1 Metabolism system of Paper II. Oxidative stress occurs when plants experience "stress" such as a drought or weather changes. This integration shows that under stress, plants deplete glutathione, resulting in the accumulation of formaldehyde (published in *American Journal of Plant Sciences*).

Paper IV: Shows that GM soy is different from non-GM soy based on the differences in the levels of glutathione and formaldehyde. We found in the GM soy, the Roundup Ready version, five molecules are disturbed, based on data from actual wet lab experiments. This molecular disturbance causes oxidative stress, which (as shown from Paper III) results in C1 Metabolism (from Paper I and II) being disturbed, resulting in glutathione being depleted, and formaldehyde accumulating (published in *Agricultural Sciences*).

Hansen: The research effort is now in the midst of collecting transgenic and non-transgenic varieties of soy. John Fagan, who is part of this effort, has access to soy plants but they are a bit old. The goal is to get the freshest supply of soy from recently harvested plants. The harvest of Argentine soybeans occurs in April to June. In September, the US harvest comes. By testing at harvest time, it is possible to have access to freshest transgenic and non-transgenic materials. As part of that testing, the standards for testing will be defined. None of the people are attacking the research, done by Dr Ayyadurai and his team, in the typical manner when one publishes a systems paper. People typically tend to question the model and rate constants and molecular pathways. No one is questioning the rate constants, or the thoroughness of the research in those four papers. No one is questioning how the modelling was done, and source of those papers. The only question is how the testing will be done. We believe that setting standards, so anyone can replicate and validate these experiments, within that standardised framework is extremely important to such testing.

Ayyadurai: Those standards are what is missing in the scientific field of GM research, and the reason for the ongoing controversies. Without those standards, results from our testing are guaranteed to be questioned. So, as a part of defining those standards, we want to bring together people from both sides, pro- and anti-GM, into an International Standards Committee that, openly and transparently, defines the standards within the framework of systems biology. This need for standards is one of the main conclusions of Paper IV. In the US, given how the system is set up, it is very difficult to even do such testing today. In fact, one may violate the licensing laws of GM seed manufacturers if one tries to test without their consent. We want to use this opportunity to perform such testing in an open, transparent manner, based on Standards.

What do you have to say about the charge that your paper was published in a 'pay-to-play' journal or of somewhat not established repute? Surely you must have known your credibility would have been far higher if a reputed journal had published it.

Ayyadurai: Let us first talk about reputed journals and non-reputed journals, because there's an assumption here. Who's deciding which is reputed and which is not? Randy Sheckman, an eminent scientist who won the Nobel Prize in Medicine and has published extensively in major and "reputed" journals such as *Nature*, *Science* and *Cell*, wrote a scathing article exposing how these major journals are damaging science based on the false measure of "impact factor" and the collusion that takes place to promote their journals as a brand. Reputed media organisations such as *The Guardian* and *The Hindu* have shared Scheckman's exposition. Scheckman believes that "There is a better way, through the new breed of Open Access journals that are free for anybody to read, and have no expensive subscriptions to promote. Born on the web, they can accept all papers that meet quality standards, with no artificial caps. Many are edited by working scientists, who can assess the worth of papers without regard for citations. It is the quality of the science, not the journal's brand that matters."

Open Access journals are the future, particularly because of the massive online audience. Thousands of journals, many of high repute, are Open Access. Before Open Access, the reader or poor graduate student had to pay $30, $40, $100 or more to download a single paper. Now the reader gets it for free, and it allows far greater access. Therefore, saying someone's research is "Pay to Play" is essentially a derogatory way of characterising Open Access, to arbitrarily put down the findings of a paper one doesn't like. In fact, MIT and Harvard, and the biggest institutions now support Open Access because it is becoming too expensive for the end-reader. So, yes, the authors pay. But to dismiss the quality of all research papers published in those journals as "Pay to Play" is the same as dismissing all papers in *Nature*, *Cell* and *Science* based on the collusion that Sheckman has exposed.

We chose these journals because that is where we saw other leaders, even those that disagree with us, publishing. The journals were Open Access, and since we were confident our work was high-quality, we wanted to ensure that as many people as possible in the field got access to our work. In fact, we've now had nearly 40,000 — and growing — accesses of our papers, when a typical paper gets only 1,000 views at best.

What you are basically saying is that people you violently disagree with have published in the very same journal, which is not exactly a great advertisement for the journals.

Ayyadurai: Two of four papers were published in *Agricultural Sciences* and the other two in *The American Journal of Plant Sciences*. Monsanto and USDA, as well as multiple departments of the University of Florida in Gainesville (UFG) have published in these journals.

As a systems biologist, I typically publish in engineering and biomedical sciences journals. The important point here is that the foundational CytoSolve systems biology methodology, used across all our papers, has also been published in multiple peer-reviewed journals such as *IEEE*, CELL's *Biophysical Journal*, etc., and cited by many other major journals including the "eminent" and "reputed" *Nature*. Remember, no one is disputing our methodology. What we did experience, however, was deliberate disinformation to distract the public and other scientists, to dismiss the findings of our work by attacking the reputation of the journals. Kevin Folta, representing himself as an "unbiased scientist", is the one who raised this issue, but he should probably attack his own colleagues at UFG, his home institution, who've also published multiple times in the journals we published in. This is just irrational behaviour. Mr Folta, by the way, is far from being an "unbiased scientist". Recent and alarming evidence in the *The New York Times* — documented across hundreds of emails, now made public following a freedom-of-information request — shows that Mr Folta was paid by Monsanto and worked closely with their public relations agency to actively spread pro-GM information. It's deplorable and exposes the most egregious academic collusion. He led the rabid attacks on our work in the blogs of a not-for-profit organisation called "Genetic Literacy Project", which is also widely known to be favourable for genetic engineering and conventional agriculture.

Randy Scheckman doesn't have this kind of baggage, and yet he is saying that "eminent" journals like *Science*, *Cell* and *Nature*, which he himself has published in, are damaging science. Who are you going to believe? The real issue, therefore, is the quality of our research. Our work did go through a peer review process. We got feedback. We got comments. Moreover, we have many eminent international scientists, including from Harvard and MIT, who are signatories in support of our findings as well as the systems biology approach we took.

Does it surprise you that a body like the USFDA has not responded to your work?

Ray Seidler: The FDA is a regulatory body and doesn't really respond or comment on published scientific work. That is really not in their purview. Remember, the FDA also has not taken any official position on GM foods, but rather provides guidelines, such as substantial equivalence, from which they perform "safety consultations" and allow manufacturers to be self-regulating.

Hansen: This is something that is often forgotten and not explicitly shared in the media. There is a big myth that the USFDA regulates and does safety assessment of GM foods. This is simply not true. The fact is that the FDA does not take a position on the safety of GM foods. A GM manufacturer simply self-reports the safety analysis of their product versus the non-GM counterpart, and the FDA simply sends them a standard letter, based on a "safety consultation", to acknowledge the self-reported safety results. On the FDA website, you can see these standard "safety consultation" letters, representing over 101 consultations, which have been completed to date.

Ayyadurai: That typical USFDA letter issued to the "Company" has a consistent paragraph, which clearly shows the self-reporting nature of this process for the GM product created by the company. Here is an exemplar paragraph from those letters:

"Based on the safety and nutritional assessment the Company has conducted, it is our understanding that the Company has concluded that food and feed from GM product are not materially different in safety, nutrition, composition, or other relevant characteristics from food and feed from apples currently on the market, and that GM product do not raise issues that would require premarket review or approval by FDA… It is the Company's continuing responsibility to ensure that foods marketed by the firm are safe, wholesome, and otherwise in compliance with all applicable legal and regulatory requirements."

The FDA simply blesses the self-reporting results for the particular GM product, and the USFDA does neither safety assessment testing nor verify the test results of the company.

Hansen: China, for example, in November 2013 decided it was no longer going to import GM corn from the US, because China had not authorised the import of a particular variety until they could do their own safety assessment. Since the US had not done any safety assessments, this made it much more difficult for the US to complain to the World Trade Organisation (WTO) that China was setting an artificial trade barrier… the truth is that the US and the FDA do not do safety assessment of GM foods that are compliant with Codex guidelines.

But the FDA says that it clears these products in terms of allergenicity, toxicity. Also that nutritionally, GM products are the same as conventional ones.

Seidler: The FDA does not carry out allergenicity or toxicity assessments on GM foods. The US has no safety assessment model for GM but provides a "safety consultation". The FDA does not carry out analysis to say whether a GM product is substantially the same as the non-GM version. The reason other countries are stopping imports of US GM products is because the US methods for safety are inadequate relative to international standards... a loosey-goosey approach and, at best, unscientific relative to real biosafety assessment. The USFDA is not even close to commenting on safety of GM foods.

Hansen: There is global agreement that there should be safety assessment for GM products. The global standard comes from Codex Alimentarius, which is the United Nations food standard agency jointly run by the WHO and the FAO. From 2000 to 2008, Codex convened an intergovernmental taskforce for foods derived from modern biotechnology. The taskforce met in Japan during this period to have a global process for risk analysis of modern biotechnology. There were several documents on how to do safety assessment of foods derived from genetically engineered plants, animals and micro-organisms. In 1995, when WTO was set up, any food standards or guidelines, etc., from Codex were considered to be trade legal. This gave a country the legal right not to import GM products if they had not been assessed for safety in that country. Since 2003, when Codex approved the first standard for foods derived from genetically engineered plants, the US has been unable to meet the global standards for such safety assessment of GM products.

You raised Codex. One of the things Codex does is labelling. In this connection, what about the legislation in Vermont in favour of mandatory labelling of GM food? Although it is still pending, do you think other states may join the campaign in the US?

Hansen: You are right. Food labelling is part of Codex. Sixty-four countries, including India, require labelling of GM food products. Over 90 per cent of the American public wants labelling. In the last two years, three states — Connecticut (CT), Maine (ME) and Vermont (VT) — have passed mandatory labelling laws, but in CT and ME they don't go into effect until four other states pass such laws. The VT bill passed in 2014 and was challenged in Vermont federal court by Grocery Manufacturers Association (GMA), with support from big agribusiness. Their lawsuit failed in April 2015, and the GMA is appealing it to a higher court. Vermont is set to start labelling in 2016, unless there is further court action. While all this was taking place, a bill was passed in the US House of Representatives to make it unlawful for states to require GM labelling in July 2015. Critics have dubbed this bill the DARK (Deny Americans the Right to Know) Act. This Act now proceeds to the US Senate for debate. This bill is a desperate move by the biotech and food industry to stop the labelling movement. There are also bills pending in three other states: New York, Massachusetts, and Rhode Island to enact labelling at the state level.

Where do you see India in this context?

Ayyadurai: As of today it is inconclusive, according to the consensus of scientists globally, whether GM crops are safe or not. The January 2015 paper (published in *Environmental Sciences Europe*), of which Dr Hansen is one of the co-authors, gathered 300 signatories including scientists from India, (and) clearly concluded that there is "No Consensus on GMO safety". In fact, in our opinion, the Indian scientific community, relative to American scientists, has been far more prudent on GM crop safety. In the Indian Parliamentary Committee Report of 2009 and the Indian Supreme Court Technical Expert Committee (TEC) Report of 2012, Indian scientists concluded the following key points:

India should not be using GM crops until at least ten years of safety assessment are done;

Except for the Bt variety (cotton), currently approved, any new Bt variety should also go through proper development and safety standards over ten years;

The US has huge factory farms. India is still 70 per cent small farms. The use of herbicide-tolerant GM crops does not make any sense in the Indian context; and, finally,

Given the biodiversity of crops in India, there should be a ban on all GM crops because it could significantly affect this biodiversity from GM crop contamination, and this will be irreversible for India.

Given the relatively more open and conducive environment for GM science in India, we are working to conduct the first meeting of International Standards Committee in India, to develop the standards for objective safety testing of GM crops versus their non-GM counterparts. We think the Indian scientific community, as well as the Indian media are currently far more open to discuss this in an objective and scientific manner relative to the US, in which lobbying and moneyed interests influence and control major scientific and academic institutions to disseminate propaganda. One such propaganda is that third world and developing nations such as India and Africa must have GM crops since they don't have enough arable land.

Yadav: I can speak specifically about India. The truth is India has enough arable land. With 157 million hectares, India holds the second-largest arable land in the world. We are also the second-largest producer of foodgrains. What India needs is irrigation technology, better education for farmers to increase productivity of crops, as well as building the capacity of stakeholders to understand the market. India, for example, has already taken a lead in organic agriculture... Sikkim's initiative for becoming a 100 per cent organic state is an example. This can give India a competitive advantage. Instead of going for GM crops, India needs to focus on enhancing productivity. The argument that India needs GM crops because of declining land and rising population is simply not correct. Vast tracts have not been brought into cultivation in the northeast of India.

Hansen: Indian scientists have been far more cautious and wise on the issue and reflect the global opinion, as against the US, which is allowing massive use of GM crops without any real safety assessment that complies with international

guidelines.

But what are the alternatives? We have new risks every year — climate change, diminishing productivity. And the returns from the Green Revolution are diminishing?

Yadav: There are many alternatives, and we need to move to real science, engineering and public policy to implement those alternatives. Given that there is no consensus on the safety of GM crops and given that the Indian scientific community has clearly said that it is premature to grow them in India, we need to address systemic issues such as farmer training, productive use of existing land, irrigation, and better mechanisation. GM crops are not a necessary part of this solution; in fact, they and the massive use of pesticides may likely be key contributors to the risks you noted such as destruction of soil, diminishing productivity and the need for more water. In fact, there is growing evidence that GM crops, Bt cotton in India, for example, require more water than the non-GM variety. Why would a developing country like India, where water is a precious resource, want to go for more water-consuming crops?

Are we exaggerating the power of the pro-GM media and playing down the power on the other side? At the end of the day it is always easier to raise an alarm.

Hansen: What we are starting to see is that major food companies are adjusting to the consumer's authentic demand for organic, less-processed and non-GM foods. In fact, even Kraft foods, based on this growing demand, decided to stop using preservatives and food colouring. From pure business considerations, food suppliers are listening to the consumers and adjusting their products. Chipotle, one of the fastest growing restaurants, is going to stop using GM ingredients, also in response to such public and consumer feedback and demand for healthier foods. The pro-GM folks, however, have resorted to massive disinformation in the media to try to reverse this tide of public opinion.

Seidler: The key point is that the broad mass of the American people are against GM, and want to see labelling. They don't want preservatives, and they don't want damaging chemicals in their food. The recent declaration by the World Health Organisation's International Agency for Research on Cancer (IARC) that glyphosate is a probable human carcinogen has resulted in limitations and/or bans of glyphosate in numerous countries. More recently a similar declaration of glyphosate carcinogenicity was announced by the California Environmental Protection Agency. This follows on the heels that glyphosate is omnipresent in virtually all GMO crops, foods, water, air, human urine, and even human breast milk. Such declarations have added significantly to this groundswell of public demand for organic and healthy foods.

Ayyadurai: It is in reaction to this groundswell that the pro-GM lobby has been spending massive amounts of money on using the media to misinform the public. The recent disclosures, in the *NY Times*, of Monsanto and its PR agency directly funding and collaborating with the University of Florida at Gainesville and the Chairman of its Horticultural Department, in creating propaganda to deliberately manipulate public opinion, exemplifies this desperate behaviour in a very unfortunate and dangerous way.

Some form of genetic modification takes place in nature and some of it occurs through breeding. So should there be a big deal made about the targeted genetic modification taking place with GM foods?

Seidler: Let's start with why there are major differences between recombinant genetic engineering, what we refer to as "genetic modification" (GM), and natural plant breeding. They are entirely different. The term "genetic modification" originally was used in Europe to refer to human-induced recombinant genetic engineering, and then began to be misused in a dilettante manner in the US, to broadly refer to the genetic changes that occur during natural plant breeding. And this is very misleading, as it allows those in favour of GM to confuse the public by saying that since GM is just another form of natural plant breeding, GM is safe.

With regard to GM (genetic engineering), to be clear, this typically requires a sterile laboratory environment and typically involves the asexual transfer of three, four or five (more or less in that range) genes, typically from one or more organisms, to produce a new product that is not natural. This means that the resulting new product has never been found, discovered or evolved naturally on the planet. Whereas, during the natural process of sexual plant breeding, there is a complete transfer of up to 20,000 genes, and the resulting organism is a natural product and a natural complement. We should not, therefore, be too surprised that recombinant genetic engineering of DNA, GM, disturbs the natural biochemical and physiological parameters in of itself. To me that is what is exciting, which Shiva's research has uncovered, using a systems biology approach, and shows that GM is substantially different from the natural process of plant breeding. So when you read or hear that genetic engineering, GM, is comparable to natural breeding, it is simply not true.

Roughly, 3-4 per cent of the arable lands on the planet have genetically engineered, GM, crops. The other 96-97 per cent of the crops on arable land is the result of natural processes that occur from pollinators that are wind or other natural events and, on occasion, through human intervention via plant breeding on a magnitude where 10,000 to 20,000 genes are transferred. This has been the natural process for millennia, but that is completely different from GM.

Hansen: By the way, except in the US, there is a clear consensus globally that GM is different from natural plant breeding. There's no debate on this issue as long as we properly agree that GM refers to the genetic engineering process/biotechnology as defined in the international Codex guidelines, which are referenced by WTO.

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