Food and Agriculture Organization
of the United Nations

Safety of novel food and genetically altered crops What would science-based regulation look like?

Seminar by Andrew Bartholomaeus, Ph.D.

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Abstract

On 13 October 2015, a seminar by Dr Andrew Bartholomaeus, the former General Manager of the risk assessment branch of the Food Standards Australia New Zealand (FSANZ), entitled "Safety of novel food and genetically altered crops - What would science-based regulation look like?" was held at headquarters of the Food and Agriculture Organization of the United Nations (FAO). Dr Bartholomaeus discussed general principles of food safety regulations emphasizing the fact that the "natural" plant genome is highly plastic and "natural" crops are genetically unstable, thus sound regulatory frameworks should take this fact into consideration. The scientific consensus around the safety of new and established biotechnology-based breeding is stronger than any other scientific issues around food regulations. With our current knowledge, wide spread insertions, deletions or Single Nucleotide Polymorphisms (SNPs) occurring frequently and randomly in nature have never produced a de novo toxin in a non-toxic crop, but somehow when these same processes are employed in a controlled manner in plant breeding programs they are strictly regulated with extensive safety assessment requirements. On the other hand, known toxins already present in a "natural" crop that can be up regulated due to stress related to pest pressure, climate, environment and agronomic practices, are not in the usual scope for the safety assessment requirements. This leads to disproportionate regulatory imposts, and misallocation of limited regulatory resources, when considering the reality based impacts on public health and food security. Dr Bartholomaeus suggested to FAO that they consider organizing expert consultations to discuss the needs in risk-based regulatory framework in the context of biotechnology within the spectrum of comprehensive plant genome plasticity. Video of the seminar is also available on YouTube at http://tiny.cc/Dr_Bartholomaeus_Video.

Keywords
genetically modified foods; novel foods; risk assessment; biosafety regulations; FAO

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Acronyms

DNA	Deoxyribonucleic acid
FAO	Food and Agriculture Organization of the United Nations
FSANZ	Food Safety Standard Australia and New Zealand
FSTN	Food Safety Technical Network
GM	Genetically Modified
GMO	Genetically Modified Organism
NBT	Natural Bob Tail
SNP	Single Nucleotide Polymorphism

Acknowledgement

FAO would like to express its appreciation to Dr Andrew Bartholomaeus, the speaker, for his expertise and experience shared during the seminar. The seminar was organized by Masami Takeuchi (FAO) under the general guidance of Markus Lipp (FAO) and chaired by Gouantoueu Guei (FAO). Technical inputs from several FAO colleagues, namely Cornelia Boesch (liaison with the FAO Food Safety Technical Network) and Roberto Sciotti (the technical assistance in video production) are also gratefully appreciated. A special thanks also goes to Kosuke Shiraishi, an intern, for various administrative assistance. For further information about the seminar, contact Masami Takeuchi at Masami.Takeuchi@fao.org. The report of the seminar (present document) and the presentation file are available online at http://tiny.cc/Dr_Bartholomaeus_Seminar. The video of the seminar is available online at http://tiny.cc/Dr_Bartholomaeus_Video.

Speaker

Adjunct Professor Dr Andrew Bartholomaeus is a toxicologist with a background covering a broad spectrum of regulatory toxicology including human and animal pharmaceuticals, nanotechnology, agricultural chemicals and food safety. Prior to his retirement from the Food Standard Australia New Zealand (FSANZ)[1], he was the General Manager of the risk assessment Branch of the Agency. He currently spends the majority of his time providing training and development to food regulators in the East and South East Asian area across the broad range of food safety issues including the regulation of novel food and biotechnology.

1. Welcome remarks by Mr Gouantoueu Guei, Senior Technical Officer, Agriculture and Consumer Protection Department, FAO

Mr Gouantoueu Guei, Senior Technical Officer of the Agriculture and Consumer Protection Department welcomed Dr Andrew Bartholomaeus and the participants by stating that he was delighted to welcome such an experienced speaker to discuss an interesting subject. He was pleased to inform that the Food Safety Technical Network (FSTN), which is the framework in organizing this seminar, is one of the most active technical networks in FAO. He stated that the traditional and conventional techniques such as plant selection and breeding have been used to modify the plant genome for years. However, modern technologies including genetic modification have been generating a lot of debates and concerns about the potential risks associated to those technologies. He stressed that science should be the basis for the evaluation of the risk associated with the technologies and many questions including technical issues and methodologies that are related to regulatory decisions need to be addressed. He concluded his remarks by wishing that this seminar and discussions would be fruitful for all the participants.

2. Seminar “Safety of novel food and genetically altered crops - What would science-based regulation look like?”

[1] Link: http://www.foodstandards.gov.au/Pages/default.aspx

2.1. Introduction

Dr Bartholomaeus started the seminar by introducing himself, stating he has been a toxicologist for the last 20 years and was running the risk assessment branch of the national authority, thus he has broad perspectives on food safety. When dealing with nanotechnology, biotechnology and food irradiation, food regulators look at the novelty, asking what is it that requires a different approach in regulating them. Meanwhile, it is usually the case when new technology is developed; enthusiasm comes in first with a high level of excitement and expectations, then "what if" follows. This "what if" generally leads to extensive regulations requiring a tremendous amount of effort and costs, and eventually it kills or inhibits the technology. And once again, it is usually the case regulators ultimately find the fact that the "novelty" that they are seeking is largely an extension of something that is already in the "natural" products. Many unintended chemical changes following food irradiation, for example, were found to be the same as the changes that occurred by "conventional" methodologies, including cooking.

In the area of biotechnology, it is true that the risks of GMOs were incompletely explored 15 years ago. However, so much knowledge on biotechnology and natural plant genome plasticity has been accumulated now and many scientific issues have been comprehensively resolved, thus it can be said that the situation is different now.

Nowadays, one of the interesting issues on biotechnology is that there is a trend for people to be concerned considerably more about food than pharmaceuticals. For more than a decade, biotechnology has been applied in the pharmaceutical industry and people accept intravenous administration of GM drugs into their bloodstream. Another issue that is prominent is that today's issue is not about big companies such as Syngenta, Monsanto, and alike. Small projects from academia/university in emerging economies are developing various GMOs to address specific local needs and a requirement for disproportionate food safety assessment data, with the associated cost of tens of millions of dollars, is generally beyond the resources available to those small-scale developers. These recent developments bring us to consider the need for reviewing the current regulatory framework that can be seen as impacting disproportionally heavy on foods derived from biotechnology.

2.2. General principles of ethical regulation

"Ethical regulation" is something that is proportionate to the risk. For new technologies, risks generally derive from the nature of the applications of that technology and the novelty arising from those applications against the context of natural and pre-existing analogues of those outcomes. Thus, the consequences of blocking or restricting new technologies on the basis of non-scientific, vague, hypothesised harms may result in greater harm than those being avoided. Dr Bartholomaeus stressed that the regulatory debate on the new trait inserted or induced by gene modification focuses only on the understanding of the generated new trait. The current trend in regulatory debate revolves around unintended, unpredictable consequences of gene insertion or induced random mutation. However, unintended effects occur during every type of breeding, whether natural, conventional or biotechnological, so it is not particularly novel. Equally unintended is synonymous with either unexpected or hazardous. The accumulated understanding of the breadth of genome

plasticity and crop compositional variation in nature indicates that there are only very limited and quite specific, and therefore predictable, circumstances where such effects might be hazardous.

2.3. Concerns of new and existing biotechnology

There are three principle public concerns around the introduction of new traits to plants by biotechnologies. The first concern is the de novo production of high potency protein toxins. If a potent toxin were to be generated due to the gene insertion or introduction, that would clearly be a high risk. However, systemic toxicity of an ingested protein requires at least three highly specific, and quite separate and extensive, structural characteristics that would simultaneously need to be generated from the same random mutation, so this is not plausible. The second fear is of the de novo generation of biochemical machinery to produce a toxic secondary metabolite unrelated to the parent plant or the source or function of the transgene itself. As for the protein toxins, multiple coordinated alterations are required and this possibility can be discounted as implausible at most. Also, in the natural environment, all plants produce toxic (to something) secondary metabolisms as pesticides that deter or combat the plant's natural predators or diseases, such as herbivores, pests, and pathogens. The third concern is the possibility to reactivate "dormant pathways" that have been postulated to exist in plants. The postulate is that plants have metabolic pathways that no longer function because of mutations that occurred during evolution and that genetic modification has the possibility to activate those silent pathways by gene insertion or chromosomal arrangements. However, mutation of the genome is a constant process in plants and non-functional genetic material will not be maintained across generations, as its degradation would not reduce the viability of the plant. Thus "dormant pathways" will accumulate mutations progressively and with each generation will require more reverse mutation in order to activate them. Consequently this concern is also implausible and has never been demonstrated even where crops have been developed using imprecise radiation mutation techniques that cause multiple widespread mutations in the genome.

2.4. Relevance of genome plasticity

Genome plasticity is the alterable nature of plant genomes that includes single point mutations and movement of genes between and within chromosomes and even from mitochondria or chloroplasts into nuclear chromosomes. The plant genome is highly plastic and plants are naturally genetically variable. Also, phenotypic and genotypic variability in food crops due to the plant genome plasticity and environmental variability is much greater than previously recognized. Individual plants of a crop cultivated in the same field can have substantially different compositions due to microclimates, pest pressure, agricultural processes and so on. The potential risks arising from variability are related to the magnitude of that variability in comparison to that occurring naturally or in conventional breeding. Taken together with the genome plasticity, Dr Bartholomaeus showed the formulation of the relevant issues on the risk assessment of novel and genetically modified foods including how variable the phenotype is without genome plasticity and how common point mutations and transposons (jumping genes) are in nature.

2.5. Sources of variability – phenotype and genotype

Plants naturally contain a variety of toxic compounds which collectively produce the full range of toxic effects in standard toxicity testing studies. Dr Bartholomaeus explained that secondary metabolites naturally produced by plants include contact allergens, carcinogens and specific organ toxins since some of those organic compounds are produced to protect themselves from insect and herbivore predation. Compositional variability, due to environmental factors, is greater than that, secondary solely to gene insertion or alteration, since plants produce chemical compounds in response to the interaction with pest pressure, microclimates, soil variability and agronomic practices.

In addition to the phenotypic variability, plants are diverse in genotype. Previous research showed that maize diversity (1.42%) is greater than the difference between humans and chimpanzees (1.34%). More than 50 million Single Nucleotide Polymorphisms (SNPs) have been identified in maize. 85% of the genome sequence of the non-GM reference inbred (B73) was identified as transposable elements – jumping genes that move randomly across the genome. Yellow maize for example is the result of the insertion of a gene into the phytoene synthase promoter region. Gene insertions have also shown to be common in any crop that has been examined, including rice, soy and tomatoes. Thus, in the natural environment, DNA variability is a completely normal event.

2.6. Conclusions and a way forward

Dr Bartholomaeus concluded his presentation by stating that well-characterised gene insertion has never been shown to produce de novo toxins and the postulated mechanisms for such toxin production are implausible and discordant with the vast amount of data now available on natural plant genome plasticity. He stressed that looking at the current technology, there is an opportunity for smaller nations to develop the capacity to utilise biotechnology to address the specific needs and challenges of their own populations, especially niche crops that are the staple of some of the poorest and most disadvantaged people. This need will only increase as the effects of climate change and population growth increase the challenges of food production. There is a need in many smaller nations for guidance on the development and implementation of risk-proportionate, science-based, ethical regulations that both ensure food crops developed by conventional and biotechnology techniques are safe, and that indigenous crop development programs are not inhibited or prevented by the cost of disproportionate regulatory requirements.

In this regard, there is an opportunity for international organizations like FAO to consider organizing expert consultations to discuss the needs in a risk-based regulatory framework in the context of biotechnology within the spectrum of comprehensive plant genome plasticity.

3. Questions and discussions

Q1: What is the difference between GM crops produced by genetic modification (gene editing/insertion) and the effects of spontaneous mutation?

Dr Bartholomaeus: Gene insertion through biotechnology techniques utilise well-characterised existing genes with a defined function that are introduced to a well-

characterised location in the crop genome. In contrast, spontaneous mutation, or that caused by radiation exposure, generate large numbers of unknown and generally uncharacterised gene mutations. In either case, however, such mutations have never produced a de novo toxin in an otherwise non-toxic crop. Conversely, both conventional and biotechnology techniques, as well as natural variation, can cause an up regulation of the production of pre-existing toxins already present in a crop. For those crops, an analysis of the level of toxins should be a routine part of both conventional and biotechnology-based crop development.

Q2: Can random mutation reactivate pathways that had been inactivated during the plants evolution?

Dr Bartholomaeus: Pathways can be dormant in the whole plant or just in a specific tissue. Pathways dormant in the whole plant will be too degraded to be activated by random mutation, due to accumulated mutations. If it were possible, it would be a common occurrence because random mutation of the plant genome is natural and common. If the pathway is dormant because it is shut down in one part of the plant, such as the fruit, but active in other parts such as the roots or leaves, then the pathways functionality is conserved and reversal of the dormancy in the fruit for example is possible. This is what happened to make white corn yellow. Any conventional or biotechnological manipulation of a crop and common techniques such as cell culture have the potential to generate such changes. If the pathway dormant in the edible part of the plant produces toxins in other parts of the plant then regardless of the technique being used for crop development, the activity of the pathway should be assessed in the edible portion as a routine component of the development cycle.

Q3: Can we absorb DNA from plants?

Dr Bartholomaeus: No. Regardless of where the DNA has come from or how it got into the plant, it is broken down by enzymes and acids in the gut into short chains of nucleotides. Theoretically minute quantities of DNA can be taken up through immune surveillance cells in the gut called M cells, but this is presented to the lymphatic system and quickly digested by nucleases within minutes.

4. Closing remarks

Mr Guei provided his closing remarks by stating that this seminar provided opportunity for participants to understand the current discussions on the science-based regulations, on the safety of novel foods and genetically altered plants. The topic has been debated for a long time and it takes time for people to fully understand what is happening during the gene change since they need to know the scientific background. Relevant scientific information needs to be delivered to the policy makers and for this purpose, experts are expected to fill the gap between the risk assessors and the policy makers who should discuss the relevant regulations based on the scientific evidence. He concluded the seminar with thanks to Dr Bartholomaeus and participants for their valuable insights.