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3 September 2015

ENGLISH ONLY

AD HOC TECHNICAL EXPERT GROUP ON
SYNTHETIC BIOLOGY
Montreal, Canada, 21-25 September 2015

PROVISIONAL AGENDA

1. Opening of the meeting.

2. Organizational matters:

   2.1. Election of officers;

   2.2. Adoption of the agenda;

   2.3. Organization of work.

3. Substantive issues:

   3.1. Relationship between synthetic biology and biological diversity;

   3.2. Similarities and differences between living modified organisms (as defined in the Cartagena Protocol) and organisms, components and products of synthetic biology techniques;

   3.3. Adequacy of existing national, regional and/or international instruments to regulate the organisms, components or products derived from synthetic biology techniques;

   3.4. Towards an operational definition of synthetic biology comprising inclusion and exclusion criteria;

   3.5. Potential benefits and risks of organisms, components and products arising from synthetic biology techniques to the conservation and sustainable use of biodiversity and related human health and socioeconomic impacts relevant to the mandate of the Convention and its Protocols;

   3.6. Best practices on risk assessment and monitoring regimes currently used by Parties to the Convention and other Governments;

   3.7. Degree to which the existing arrangements constitute a comprehensive framework in order to address impacts of organisms, components and products resulting from synthetic biology, in particular threats of significant reduction or loss of biological diversity.

4. Conclusions and ways forward, including elements to facilitate future discussions and actions on synthetic biology under the Convention.

5. Other matters.

6. Adoption of the report.

7. Closure of the meeting.

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UPDATED REPORT AND SYNTHESIS OF VIEWS IN RESPONSE TO PARAGRAPH 7(b) OF DECISION XII/24 ON NEW AND EMERGING ISSUES: SYNTHETIC BIOLOGY

Note by the Executive Secretary

I. BACKGROUND

1. In paragraph 4 of decision XII/24,[1] the Conference of the Parties to the Convention on Biological Diversity established an Ad Hoc Technical Expert Group (AHTEG) on Synthetic Biology with terms of reference contained in the annex to the decision.

2. In paragraphs 5 and 6 of the same decision, the Conference of the Parties invited Parties, other Governments, relevant organizations, indigenous and local communities and relevant stakeholders to submit information to the relevant to the work of the AHTEG, as well as on measures undertaken in accordance with paragraph 3 of decision XII/24, including the identification of needs for guidance, and further information in response to paragraph 3(a) of decision XI/11.

3. Further, in paragraph 7 of the same decision, the Conference of the Parties requested the

(a) To make available the information submitted by Parties, other Governments, relevant organizations, indigenous and local communities and relevant stakeholders through the clearing-house mechanism of the Convention and other means;

(b) To convene a moderated open-ended online forum[2] to support the work of the AHTEG in meeting its terms of reference;

(c) To prepare an updated report on the work specified in paragraphs 3(a), 3(b) and 3(c) of decision XI/11, taking into account information submitted in paragraph 2 above and a synthesis of the outcomes of the process mentioned in (b) above, and to submit these for consideration by the AHTEG;

(d) To submit for consideration by a meeting of the Subsidiary Body on Scientific, Technical and Technological Advice (SBSTTA) prior to the thirteenth meeting of the Conference of the Parties, the peer-reviewed reports of the outcomes of the process mentioned in paragraphs (b) and (c) above.

4. In the light of the decision, the established a continuous process comprising: (a) the submission of information on synthetic biology; (b) an open-ended online forum with online discussions on specific topics of synthetic biology; (c) one face-to-face meeting of the AHTEG; and

[1] Full text of the decision can be found at http://www.cbd.int/doc/decisions/cop-12/cop-12-dec-24-en.pdf.

[2] The open-ended online forum will be open to all interested participants and continue for a finite period of time.

(d) peer-review of the outcomes of the process.3 The outcomes of this process will be submitted for consideration by the Subsidiary Body on Scientific, Technical and Technological Advice (SBSTTA) at its twentieth meeting to be held in Montreal, Canada from 25 to 29 April 2016.

5. The process was initiated by two notifications that were issued to Parties, other Governments, relevant international organizations, indigenous and local communities and other relevant stakeholders inviting them to (a) submit to the information on synthetic biology;[4] and (b) nominate experts to participate in the Open-ended Online Forum on Synthetic Biology.[5]

6. In response to the first notification, a total of 27 submissions were received by the Secretariat. Among these were fifteen from Parties, one from a non-Party, and eleven from organizations.[6]

7. In response to the second notification, a total of 235 experts were nominated to participate in the open-ended online forum. Among these, 146 were from Parties, nine from a non-Party, and 80 from organizations.

8. The Open-ended Online Forum on Synthetic Biology was launched through the Biosafety-Clearing House and a total of 402 interventions were made during the virtual discussions that took place between April and July 2015. The topics of discussion were drawn from the terms of reference of the AHTEG, as follows:[7]

(a) How to address the relationship between synthetic biology and biological diversity (moderated by from Japan);

(b) Similarities and differences between living modified organisms (as defined in the Cartagena Protocol) and organisms, components and products of synthetic biology techniques (moderated by from Mexico);

(c) Operational definition of synthetic biology, comprising inclusion and exclusion criteria (moderated by from Estonia);

(d) Potential benefits and risks of organisms, components and products arising from synthetic biology techniques to the conservation and sustainable use of biodiversity and related human health and socioeconomic impacts relevant to the mandate of the Convention and its Protocols (moderated by from Norway);

(e) Best practices on risk assessment and monitoring regimes currently used by Parties to the Convention and other Governments (moderated by Ms. Jaimie Schnell from Canada);

(f) Adequacy of existing national, regional and/or international instruments to regulate the organisms, components or products derived from synthetic biology techniques (moderated by from Kenya);

(g) Degree to which the existing arrangements constitute a comprehensive framework in order to address impacts of organisms, components and products resulting from synthetic biology, in particular threats of significant reduction or loss of biological diversity (moderated by from Ecuador).

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[3] A tentative calendar of activities for the process is available at https://bch.cbd.int/calendar_synbio.shtml.

[4] Notification SCBD/BS/CG/MPM/DA/84279 (https://www.cbd.int/doc/notifications/2015/ntf-2015-013-synthetic-biology-en.pdf).

[5] Notification SCBD/BS/CG/MPM/DA/84355 (https://www.cbd.int/doc/notifications/2015/ntf-2015-019-synth-en.pdf).

[6] The submissions are available online at http://bch.cbd.int/synbio/notifications/.

[7] The discussions under the Open-ended Online Forum on Synthetic Biology are available at http://bch.cbd.int/synbio/open-ended/discussion.shtml.

9. The present note provides an overview of the views contained in the submissions and online interventions. For a full account of all views, it is recommended to refer to the original submissions and online interventions through the Biosafety-Clearing House.[8]

10. For the purpose of this note and in accordance with the online forum, to facilitate a common understanding in the discussions on similarities and differences with LMOs, the term "components" is used to refer to parts used in a process (e.g. a naked DNA molecule), and "products" as the resulting output of a process (e.g. a chemical fragrance).

II. RELATIONSHIP BETWEEN SYNTHETIC BIOLOGY AND BIOLOGICAL DIVERSITY

11. Many submissions and online interventions noted that the relationship between synthetic biology and biological diversity must be addressed in the light of the three objectives of the Convention to ensure the conservation of biological diversity, the sustainable use of its components and the equitable sharing of the benefits arising out of the utilization of genetic resources. This could be done by examining both the potential positive and negative impacts of synthetic biology and their relevance to the CBD objectives, assessing the risks on a case-by-case basis and, where necessary, adopting appropriate risk management strategies.

12. Views on the relationship between synthetic biology and biological diversity converged in suggesting that synthetic biology may affect biodiversity at the genetic, species and ecosystems levels. However, the discussions also indicated the diverse and polarized interpretation of the relationship between the two concepts.

13. According to submissions made by several Parties, synthetic biology techniques could contribute to the sustainable use and conservation of biodiversity, but, at the same time, the components, organisms and products of synthetic biology may lead to situations that compromise the sustainable use of biodiversity and/or ecological balance.

14. In the online forum, it was further noted that the relationship between synthetic biology and biological diversity could focus on areas of concern within the CBD context. It can be described by the potential direct and indirect impacts that these new organisms and components could have on conservation and sustainable use of biological diversity. The risks and potential impacts of the relationship should be assessed prior to any introduction to the environment, taking also into account risks to human health, small scale farming systems and their contribution to biological diversity and ecosystem function, food security, livelihoods and related socioeconomic considerations, indigenous peoples and local communities, including cultural aspects.

15. With regard to the third objective of the CBD, it was noted in the online forum that the fair and equitable sharing of benefits arising out of the utilization of genetic resources must be considered in the light of the development of the many components of synthetic biology, their applications and possible effects on biodiversity. It was noted that the objective of fair and equitable sharing of benefits arising from the use of genetic resources may lose its purpose, as use of components, organisms and products from synthetic biology may replace the need for and use of natural genetic resources. A participant in the online forum also noted that a profit-driven approach to synthetic biology does not necessarily support the fair sharing of costs and benefits between developed and developing countries, and that this situation has been exacerbated by control over the techniques of synthetic biology by a limited number of stakeholders, most of whom are driven primarily by a profit motive rather than by ecological perspective.

16. Views were divergent with regard to which components, organisms and products could pose risks to biodiversity. While some participants of the online forum suggested that the discussion on the

[8] Submissions of views on synthetic biology by Parties, other Governments and organisations are available at: http://bch.cbd.int/synbio/notifications/; Discussions under the Open-ended Online Forum on Synthetic Biology are available at: http://bch.cbd.int/synbio/open-ended/discussion.shtml

relationship between synthetic biology and biodiversity should focus on all components, organisms and products of synthetic biology, others suggested a limited focus on the components, organisms and products of synthetic biology that are capable of replicating or reproducing and could be released into the environment to determine their potential positive or negative impact on biodiversity.

17. It was also noted that a lack of scientific underpinning to ecological and social impacts in the application of synthetic biology processes poses a key issue in the discussion on the relationship between synthetic biology and biodiversity. An increase in the complexity and range of synthetic biology tools and techniques may also lead to an increase in the uncertainty and unpredictability of their outcomes, making it harder to predict their effects on biodiversity, leading to the need for stricter measures to prevent damage to biodiversity.

18. In further discussions on the uncertainty about the safety of the components, organisms and products of the processes and outcomes of synthetic biology, several Parties, organizations and participants of the online forum called for the application of the precautionary approach contained in Principle 15 of the Rio Declaration on Environment and Development.

19. There were also divergent views in the discussions on whether or not the relationship between synthetic biology and biodiversity should focus on the output from the process (i.e. an organism or product derived from synthetic biology) or on the process itself (i.e. the techniques used). The proponents of the former noted that, if a synthetic biology organism poses a risk to biodiversity, this risk would clearly lie in the characteristics of the organism (e.g. invasiveness, ability for horizontal gene transfer, risk for human beings or the environment), regardless of the techniques used to produce the organism. On the other hand, the proponents of further discussions on the process itself argued that the changes in some of the organisms and products may not be easily detectable and an assessment of the impacts on biodiversity can only be performed if the process is taken as a starting point. In this regard, there was also support to reconcile the two approaches by focusing the future debate on the relationship between synthetic biology and biodiversity on both the outputs and the process in a mutually supportive manner rather than as competing elements of the debate.

20. Some participants in the online forum also noted the challenge in establishing the relationship between synthetic biology and biological diversity in the absence of an operational definition of synthetic biology.

21. There were also participants who noted that it is premature to discuss the relationship between synthetic biology and biodiversity since an agreement has not been reached on whether or not synthetic biology is a new and emerging issue for conservation and sustainable use of biodiversity. Furthermore, some participants also noted that since no one fully understands the risks posed by synthetic organisms to the environment, there are challenges as to what kinds of information is needed to support rigorous risk assessments, or who should collect such data.

22. Finally, in discussing the relationship between synthetic biology and biodiversity, there were suggestions that the potential damage resulting from organisms, components and products of synthetic biology techniques also needs to be addressed through a liability and redress regime.

III. SIMILARITIES AND DIFFERENCES BETWEEN LIVING MODIFIED ORGANISMS (AS DEFINED IN THE CARTAGENA PROTOCOL) AND ORGANISMS, COMPONENTS AND PRODUCTS OF SYNTHETIC BIOLOGY TECHNIQUES

23. There was general agreement in the submissions and online interventions that synthetic biology builds on the advances in molecular biology and biotechnology. However, some elements of synthetic biology which set it apart from other more "conventional" approaches of modern biotechnology initiated intense debate in the discussions.

24. It was noted in a submission that when the terms "components" and "products" of synthetic biology are used to refer to non-living entities, they have more in common with chemical substances. As such, similarities and differences should be drawn between LMOs and the organisms developed through synthetic biology techniques but not between LMOs and the components and products of synthetic biology. In this context, it was noted that some complex living systems resulting from synthetic biology are not always organisms, but rather belong to other structural levels such as organs, tissues, cells or proto-cells.

25. Many submissions and online interventions noted that the techniques that are described as synthetic biology form a continuum of advances in biotechnology tools and techniques, and may equally be described as techniques of modern biotechnology, gene technology or genetic engineering, in particular those applications of synthetic biology that are closest to commercial scale application. Some of the similarities between synthetic biology and modern biotechnology that were noted in the submissions and online interventions include:

(a) Synthetic biology is a "new branch of genetic engineering" and "every organism, component and product of synthetic biology techniques is a result of genetic engineering, but not every LMO is a result of synthetic biology";

(b) Synthetic biology can be considered as "an extension of conventional molecular biology", "an accelerated and intensified form of classical genetic engineering", and that "the underlying technology makes synthetic biology and classical genetic engineering [...] basically the same";

(c) Current development of living organisms through techniques of synthetic biology relies on the use of techniques of modern biotechnology, which are combined with other tools such as bioinformatics, nanotechnology, robotics, etc. Therefore, living organisms that are currently being developed through synthetic biology can also be considered as LMOs as per the definition of the Cartagena Protocol, since they result from the application of techniques of modern biotechnology. This would also include living organisms derived from existing ones through the incorporation of xeno-genetic materials;

(d) The Cartagena Protocol broadly defines "living organism" as one that is "capable of transferring or replicating genetic material", while the Convention defines "genetic material" as including nucleic acids from "plant, animal, microbial or other origin", consequently, neither organisms created "de novo" nor xeno-systems may be excluded from the Protocol's scope.

26. On the other hand, there were also submissions and online interventions that were of the view that synthetic biology is qualitatively different from modern biotechnology. The following paragraphs highlight some of the noted differences between LMOs and organisms developed through synthetic biology:

(a) The differences between an LMO and an organism developed through synthetic biology lie mainly on the higher level of complexity of the latter. Such complexity may result from the combination of several techniques of genetic engineering to produce an organism combined with other techniques that rely on the standardization and abstraction of modular biological components. Furthermore, LMOs are organisms developed by incorporating a single or a few gene(s) of interest, whereas organisms constructed by means of synthetic biology techniques are likely to have larger segments of modified DNA or even complete novel genomes;

(b) As opposed to modern biotechnology, synthetic biology leads to the development of new biological systems that do not exist in nature. Therefore, "modification" and "re-engineering" are distinguishing factors between LMOs and the organisms developed through synthetic biology;

(c) The production of living organisms through modern biotechnology and synthetic biology is similar but the genes and nucleic acid molecules transferred into the recipient organisms differ in that nucleic acids transferred through modern biotechnology exist in nature but not those transferred through

synthetic biology. Therefore, some techniques of synthetic biology may or may not be readily classified as "*in vitro* nucleic acid techniques";

(d) In the future, with further technological advances, entire new genomes will be generated by designing new genetic codes. These new synthetic organisms may no longer be considered as "genetically modified" and may be completely different from the current LMOs.

27. In summarizing the apparent divergence of views, one submission noted that current techniques of synthetic biology do not develop organisms that are entirely synthetic. Rather, they create artificial genetic material, which is then inserted into bacterial cells from which the original genetic material has been removed. Therefore, it is important to highlight that such organisms are LMOs obtained through modern biotechnology as per the Cartagena Protocol on Biosafety. However, it remains a matter of interpretation whether or not living organisms resulting from certain areas of synthetic biology research, such as the synthesis of entire organisms, xenobiology or manipulations that lead to heritable characteristics without the creation of "novel combinations of nucleic acids", fall within the scope of the Cartagena Protocol on Biosafety.

IV. OPERATIONAL DEFINITION OF SYNTHETIC BIOLOGY, COMPRISING INCLUSION AND EXCLUSION CRITERIA

28. It was widely recognized, from among the submissions, that synthetic biology is a broad term which encompasses and/or is used to refer to a wide range of disciplines, techniques, potential applications and end products.

29. In discussing the steps towards an operational definition of synthetic biology, the majority of submissions and interventions in the online forum recognized the need for a definition that will support Parties' efforts in policy-making and risk assessment, and which is sufficiently broad to include new developments in the field of synthetic biology. As such, it was noted that defining synthetic biology is not merely an academic exercise, but rather a necessary step to determine if synthetic biology is objectively unique from other already-existing areas, and whether or not the outcomes of its research and development require new approaches to regulation.

30. Many of the interventions made in the online forum indicated that without an agreed definition it would not be possible to discuss the potential benefits and hazards of synthetic biology under the Convention's umbrella. However, one Party, in its submission, also noted that although having a definition for synthetic biology could facilitate enabling a rational discussion, the adoption of such a definition must not be seen as a prerequisite for the discussion on the potential regulatory and risk assessment challenges of synthetic biology.

31. There were several submissions and online interventions that were of the view that the definition of LMO under the Cartagena Protocol can be readily applied to living organisms developed through synthetic biology. In this regard it was noted that, as per its definition in the Cartagena Protocol, an LMO must be "living" and contain a "novel combination of genetic material" as a result of the "application of modern biotechnology", and that these three criteria only expressly exclude non-living entities created by synthetic biology approaches while being sufficiently broad to encompass all living organisms developed through synthetic biology. As such, those interventions and submissions noted that, as a starting point in defining synthetic biology, it would be useful to determine which, if any, aspects or techniques of synthetic biology would fall outside of the broad definition of "modern biotechnology" as per the Cartagena Protocol.

32. There was also ample support among the participants in the online forum to the operational definition recently agreed upon by the Scientific Committee on Emerging and Newly Identified Health Risks of the European Commission, which reads "SynBio is the application of science, technology and engineering to facilitate and accelerate the design, manufacture and/or modification of genetic materials in living organisms", as an appropriate basis for further discussion.

33. The following are some additional concrete proposals for definitions as contained in the submissions and online interventions:

(a) "Synthetic biology is a science of constructing biological parts, pathways and organisms towards useful social outcomes";

(b) "Synthetic biology designs non-living and living useful products using newly designed synthetic or naturally derived DNA and non-DNA molecules in novel configurations that are not found in nature";

(c) "Synthetic biology is the planned design and construction of specific biochemical and biological systems, as well as the synthesis of molecules and the development of biological components and organisms, through genetic and biological engineering and bioinformatics, to perform new functions or to improve the design of existing natural biological systems to optimize their useful applications";

(d) "Synthetic biology is a scientific strategy that combines knowledge from various disciplines such as molecular biology, biochemistry, systems engineering, genomics, protein design, directed evolution, genetic engineering, nanotechnology, mathematics, physics, cybernetics, mechatronics, bionics, etc. and the use of modern techniques (including engineering and sciences), which integrates design, build artificial biological systems (organisms, molecules, etc.) and redesign natural biological systems";

(e) "Synthetic biology describes the application of various techniques of modern biotechnology that exercise control in the design, synthesis or redesign of new biological organisms, parts, devices and genetic systems at the organismal, cellular or sub-cellular level for applied purposes. [...][9] Synthetic Biology is particularly, but not exclusively, associated with chemical synthesis or alteration of genetic sequences and nucleic acids, genome editing techniques and an engineering-based approach to the construction of living organisms resulting in a range of traits, applications and products, living and non-living, and of differing characteristics";

(f) "Synthetic biology aims to design and engineer biologically based parts, novel devices and systems as well as redesigning existing, natural biological systems";

(g) "Synthetic biology is an emerging area of research and development involving novel combinations of methods, techniques and practices drawn from a range of disciplines directed to understanding, designing and engineering biological components, organisms and products";

(h) Synthetic biology includes any "experimental attempts to explore new directions with modified organisms or proto-organisms (i.e. protocells)".

34. In discussing a definition of synthetic biology, it was also noted that it is "difficult and presumptuous to attempt to develop a formal definition of synthetic biology, let alone inclusion and exclusion criteria", "scientific advances would quickly render any definition obsolete", and the "application of strict definitions could unduly restrict or stifle cutting-edge research and development". There were also those who cautioned that the establishment of inclusion and exclusion criteria could lead to situations where products are excluded from regulation or oversight in situations where it is legitimately needed.

V. POTENTIAL BENEFITS AND RISKS OF ORGANISMS, COMPONENTS AND PRODUCTS ARISING FROM SYNTHETIC BIOLOGY TECHNIQUES TO THE CONSERVATION AND SUSTAINABLE USE OF BIODIVERSITY AND RELATED HUMAN HEALTH AND

[9] The author of this proposal suggested that a list containing techniques and approaches commonly used for synthetic biology could be annexed to the definition.

SOCIOECONOMIC IMPACTS RELEVANT TO THE MANDATE OF THE CONVENTION AND ITS PROTOCOLS

35. According to several submissions and online interventions, the components, organisms and products of synthetic biology are expected to produce similar impacts, both positive and negative, as classical genetic engineering on biological diversity. The impacts of synthetic biology, however, are expected to be broader and more intense due to the ability of synthetic biology to engineer more complex systems for use in a wider range of applications.

36. Some of the identified potential benefits of synthetic biology as a means to promote the conservation of biological diversity in areas such as bioenergy, environment, wildlife, agriculture, chemicals and health include the following:

(a) Producing sustainable sources of fuel and energy;

(b) Engineering organisms to produce useful products such as microorganisms that can produce any naturally occurring molecule (e.g. flavours, scents, dyes and pharmaceuticals) and thereby eliminating the need to cultivate large monocultures of the original source plants or animals and therefore reducing the amount waste produced during extraction and purification from the original source organisms;

(c) Improving human nutrition and health by, for example, making models for understanding and diagnosing human conditions and producing pharmaceuticals to treat and cure diseases;

(d) Reducing the area of land required for commercial cultivation, aiding in the conservation and sustainable use of biodiversity;

(e) Producing novel useful substances that are not found in nature;

(f) Designing products that will generate socially useful outcomes faster, in a more environment friendly and cost-efficient manner;

(g) Reducing environmental hazards by replacing current industrial chemical processes that are not ecologically-friendly with more sustainable and non-toxic production systems based on biological processes;

(h) Reducing pressure on certain wildlife species and restoration of populations and ecosystems through the production of synthetic products that are currently obtained from species at risk of extinction come from copies of species at risk.

37. Risks from the components, organisms and products of synthetic biology were also identified among the submissions and online interventions for their potential to affect (a) the conservation of biodiversity at the genetic and ecosystem level through, for example, direct impacts to the health and integrity of species and ecosystems, and indirect impacts arising from industrial application of synthetic biology techniques and products, (b) the sustainable use of the components of biological diversity through indirect impacts associated with the replacement of natural products, and (c) the fair and equitable sharing of the benefits arising out of the utilization of genetic resources through a shift in the understanding of what constitutes a genetic resource and implications thereof.

38. Applications of synthetic biology which involve gene-drive systems, enhanced photosynthesis, de-extinction, environmental sensors and bioremediation were identified in some online interventions as deserving close attention because of their potential to cause significant negative impacts on biodiversity and ecosystems. The identified risks include the following:

(a) Organisms developed through techniques of synthetic biology with engineered fitness advantages competing against naturally occurring organisms in the ecosystem, either through intentional or accidental introduction into the environment, causing displacement and/or extinction of existing species;

(b) Increase in mutation rates in organisms developed through synthetic biology given that the genetic material is foreign and novel and has not had time to stabilize;

(c) Increase in the occurrence of lateral/horizontal gene flow due to genome instability as compared to the natural transfer of genetic materials which has recently been reported to take place between humans, vertebrates and invertebrates;

(d) Changes in the interaction between humans and nature (i.e. cultural, social, ethical, traditional changes, among others, driven by synthetic biology techniques, could modify or affect the action and the interrelationship between humankind and nature);

(e) Outcrossing, vertical gene flow and the resulting unknown consequences, for example, to agrobiodiversity and food security;

(f) Monopoly of the technology by developed countries affecting the economy of developing countries which are based on the sustainable use of biodiversity, as well as limiting the ability of developing countries to access and perform research using components, organisms or products subject to patents and intellectual property rights;

(g) Accidental exposure to organisms or components of synthetic biology which were intended for contained use causing adverse effects to humans and other species, including risks associated with bioterrorism;

(h) Further and accelerated disruption of the relationship between mankind and ecosystems, as well as changes to biological systems and processes that naturally support mankind thereby affecting the cultural, social and economic aspects of biodiversity;

(i) Reduced confidence in the conclusions of environmental and health assessments due to higher levels of scientific uncertainty regarding the risk of organisms and products resulting from synthetic biology;

(j) Many-fold increases in the demand for biomass crops, wood and the water, nutrients and soils required for the conversion of cellulose if technologies are further advanced by synthetic biology causing serious negative impacts on biodiversity such as the conversion of forests to tree monocultures, displacement of food production, loss of biodiversity, water and soil degradation, speculative investment in land, and displacement of human populations;

(k) Possible toxic or disruptive effects on soils, food webs, pollinators and biodiversity of industrial products or enzymes (e.g. biofuels, chemicals, flavours and fragrance molecules) in the event that the organisms producing these compounds are accidentally introduced into an open environment and succeed in reproducing and establishing themselves;

(l) Spontaneous and unintentional transboundary movements of organisms developed through synthetic biology causing significant economic and ecological consequences in countries that are not prepared to take adequate measures;

(m) Decrease in agricultural genetic diversity due to a reduction in the efforts to maintain gene banks and botanical collections for the purposes of performing classical breeding since it will no longer be necessary to have individuals and make conventional crosses to introduce desirable characteristics into cultivated varieties.

VI. BEST PRACTICES REGARDING RISK ASSESSMENT AND MONITORING REGIMES CURRENTLY USED BY PARTIES TO THE CONVENTION AND OTHER GOVERNMENTS

39. A number of best practices regarding risk assessment and monitoring regimes were identified among the submissions and online interventions. They included, for example, legislations, policies and guidelines adopted by countries.

40. Several Parties, in their submissions, noted that risk assessment practices are in place that can be adapted to address the risks posed by organisms developed through synthetic biology techniques. Parties shared their experience with LMOs where risk assessments follow a science-based approach in a case-by-case basis, using comparative analysis and taking international principles and guidelines into consideration. Parties also noted that socioeconomic impacts of the commercial release of an LMO are assessed.

41. With regard to best practices regarding monitoring regimes, Parties noted the importance of regulatory schemes undergoing periodic review to ensure that they keep pace with technology developments and scientific knowledge regarding risks. Furthermore, regulators must consult peer-reviewed publications and may reassess an approved organism if new information concerning its safety comes to light.

42. It was also noted in the online interventions that a number of international organizations and initiatives exist through which countries can share, communicate and develop, as needed, international guidelines for regulatory frameworks and risk management recommendations that they may then be implemented as appropriate and in compliance with individual national statutory and governance authorities. For example, the "Environmental Risk Assessment Toolkit" of the Organisation for Economic Co-operation and Development (OECD) offers guidance on risk assessment and provides consensus information useful in a risk assessment.

43. The work done under the Cartagena Protocol for the development of the "Training Manual on Risk Assessment of Living Modified Organisms" and the "Guidance on Risk Assessment of Living Modified Organisms"[10] was also noted as examples for best practices. Other examples for best practices identified in the submissions and online interventions include the "The Principles for the Oversight of Synthetic Biology"[11] developed by the ETC Group, "*Guía para la Evaluación de Riesgo Ambiental de Organismos Genéticamente Modificados*"[12] developed by the International Life Sciences Institute of Brazil.

44. In spite of having robust risk assessment practices in place to evaluate LMOs, some Parties also noted that risk assessment approaches and protocols for organisms of synthetic biology are still in development and, hence, there is a need for specific guidelines and capacity-building opportunities to be made available as new information concerning their safety come to light and new protocols are developed.

45. The full range of best practices identified in the submissions and online interventions can be accessed through the Biosafety Clearing-House.[13]

VII. ADEQUACY OF EXISTING NATIONAL, REGIONAL AND/OR INTERNATIONAL INSTRUMENTS TO REGULATE THE ORGANISMS, COMPONENTS OR PRODUCTS DERIVED FROM SYNTHETIC BIOLOGY TECHNIQUES

46. Several submissions and online interventions noted that most of the current commercial and near-commercial applications labelled as synthetic biology involve the modification of existing organisms through the addition of genes coding for entire biosynthetic pathways and/or the modification of existing

[10] Available at http://bch.cbd.int/cpb_art15/training.shtml and https://bch.cbd.int/protocol/guidance_risk_assessment, respectively.

[11] Available at http://www.etcgroup.org/content/principles-oversight-synthetic-biology.

[12] Available at http://www.ilsi.org/Brasil/Pages/ViewItemDetails.aspx?WebId=C34AB3F5-C89B-49B3-9740-31F407A2A6FD&ListId=91D4243D-A11D-4CB9-B694-551373D9E8C5&ItemID=73.

[13] Available at http://bch.cbd.int/synbio/notifications/ and http://bch.cbd.int/synbio/open-ended/discussion.shtml, respectively.

genes and gene pathways to allow for the production of new molecules. Consequently, any organism that is produced by these means would be considered an LMO developed through modern biotechnology.

47. There was general agreement that living organisms generated through synthetic biology fall within the scope of the Convention and its Protocols, as well as under existing national biosafety frameworks. It was noted that, at the national level, Article 8 of the Convention requires all signatories to establish or maintain means to regulate, manage or control the risks associated with the use and release of LMOs resulting from biotechnology. This article is further supplemented by the Cartagena Protocol and Nagoya Protocol dealing with biosafety and the fair and equitable sharing of benefits, respectively, across national boundaries.

48. On the other hand, some research areas of synthetic biology, including gene editing, protocells and orthogonal systems, could raise potential issues with regard to the regulatory status of the resulting living organisms as they may or may not be considered LMOs as per the definitions in the Cartagena Protocol and national legislations. In this context, some submissions pointed to the need to expand the language of the Cartagena Protocol and national legislations with a view to making them fully adequate in addressing a broad range of current and future living organisms developed through synthetic biology, while others were of the view that the development of a dedicated regulatory instrument which focused specifically on synthetic biology is necessary to fully address the three objectives of the Convention.

49. There was a range of views regarding the extent to which existing international regulatory systems are adequate to address environmental, health, and societal concerns posed by the products of synthetic biology, which are themselves not "living organisms". On the one hand, some submissions and interventions noted that the products of synthetic biology, similarly to non-living products of genetic modification or biotechnology, are adequately addressed in a sectorial manner by current international regulatory regimes designed for certain end-uses (e.g. pharmaceuticals) or by regimes designed to regulate chemicals. On the other hand, some submissions and interventions noted that the current international regulatory instruments are not adequate in that they are fragmented and do not comprehensively address all concerns related to the products of synthetic biology including, but not limited to, socioeconomic impacts and the issue of liability and redress.

50. At the national level, it was noted that existing national biosafety frameworks and legislations may be applicable to synthetic biology if they treat the organisms and products of synthetic biology as equivalents to those of modern biotechnology. Likewise, existing national policies governing the exchange, distribution and commercialization of the products of modern biotechnology may also be applied to the non-living components and products of synthetic biology.

51. In summary, the majority of submissions and online interventions noted that current living organisms resulting from synthetic biology are adequately regulated within the scope of the Convention and its Protocols, in particular the Cartagena Protocol, as well as under national biosafety regulations. Nevertheless, this assertion may need to be revisited at regular intervals to account for the rapid progresses in the approaches and techniques of synthetic biology. There was less agreement with regard to whether or not existing regulations are adequate to regulate non-living components and products of synthetic biology.

VIII. DEGREE TO WHICH THE EXISTING ARRANGEMENTS CONSTITUTE A COMPREHENSIVE FRAMEWORK IN ORDER TO ADDRESS THE IMPACTS OF SYNTHETIC BIOLOGY, IN PARTICULAR THREATS OF SIGNIFICANT REDUCTION OR LOSS OF BIOLOGICAL DIVERSITY

52. In considering the current and short-term developments in the field of synthetic biology, there was a certain level of agreement among the submissions and online interventions that the principles and methodologies of risk assessment, as well as risk management measures, established for LMOs can serve as a basis for addressing potential adverse effects associated with organisms developed through synthetic biology.

53. There was also some agreement among the submissions and online interventions that, in the future, synthetic biology is likely to lead to the development of organisms that will differ fundamentally from naturally occurring ones, which will raise specific challenges and limitations with regard to risk assessment principles and methodologies that are currently applied to evaluate LMOs. As such, risk assessment methodologies that are currently in use by countries will need to be revised and adapted to ensure that the risks of synthetic biology are adequately assessed.

54. In practice, it was noted that the existing approaches of risk assessment, management and communication can be used as a basis for assessing and mitigating the impacts of organisms developed through synthetic biology techniques, provided that guidelines and methodologies are developed and made available to address the additional uncertainties and knowledge gaps. The need for a revised risk assessment framework to address the possible novel risks posed by products of synthetic biology whereby no parent organisms can be used as comparators was also noted.

55. The following further observations were made in the context of addressing the impacts of synthetic biology:

(a) Many of the current synthetic biology applications are destined for contained use and are somewhat removed from having a direct impact on the environment and biodiversity. The discussion on the impacts of synthetic biology would benefit from a focus on the potential impact of organisms that are being developed for intentional introduction into the environment and which are capable of replicating or reproducing;

(b) Risk assessors and regulators have relatively little experience considering the potential hazards posed by the intentional release of microorganisms, be they the result of synthetic biology or otherwise;

(c) In the future, organisms could be developed through synthetic biology that will fundamentally differ from naturally occurring organisms, e.g. by increasing the number of introduced biological parts, by using novel nucleic acid sequences or by using orthogonal systems. In such cases, it will be impossible to conduct risk assessments based on a comparative principle due to the lack of appropriate comparators;

(d) Due to the complexity and novelty of the organisms developed through synthetic biology, the type and depth of information that may be required to assess their risks will differ from the information typically provided by the developers for conducting risk assessments of LMOs;

(e) It will a challenge to assess the potential short- and long-term socioeconomic impacts of synthetic biology, including the impacts on traditional practices and traditional knowledge as these are usually not measurable.

56. In summary, when considering the degree to which the existing arrangements constitute a comprehensive framework in order to address the impacts of synthetic biology, the majority of submissions and online interventions noted that the methodology that is currently in use to assess the risks of LMOs can provide a basis for the risk assessment of living organisms developed through synthetic biology. Nevertheless, there is a need to revise and further develop risk assessment methodologies in order to fully address the potential environmental and societal impacts of synthetic biology.

IX. OUTLOOK AND POSSIBLE ELEMENTS OF A WAY FORWARD

57. In their submissions, a number of Parties proposed elements of a way forward for consideration in the deliberations on synthetic biology under the Convention, including the following:

(a) A system that not only encourages innovation, but also fosters an open legal framework and transparency is needed. This may lead to awareness by the public and oversight by an informed collection of governments worldwide, for environmentally sound uses of synthetic biology techniques.

The cost of health and socioeconomic impacts of processes originating from synthetic biology may be assessed and evaluated in relation to its potential to replace hazardous and polluting chemical processes;

(b) Scientific and technological developments in the field of synthetic biology must be reviewed regularly and action taken if voluntary codes or current regulatory procedures appear insufficient. In this regard, exchange between the research community, risk assessors and policymakers will be central to expanding scientific and technical knowledge and filling potential gaps in risk assessment and regulation of evolving developments. Further approaches to reconsider effective risk governance must also be taken in a global perspective, allowing international coordination and dialogue;

(c) In order to maximize potential benefits and avoid risks, and given the high level of uncertainty associated with the technologies involved, the Convention must prudently support the developments of this technology, by carefully assessing ecological and social values and by seeking to avoid unacceptable damage to species, people and ecosystems. Therefore, the use of synthetic biology must be based on a precautionary approach in line with existing decisions of the Convention of the Parties and, in particular, in accordance with paragraph 4 of decision XI/11, as well as by carrying out risk assessments on a case-by-case basis, and considering potential benefits in an evidence-based manner. Furthermore, an environmental and commercial release of organisms resulting from synthetic biology must not be performed until procedures and regulatory processes or international regulatory frameworks are in place to ensure the protection of ecological systems;

(d) Work being undertaken by other national and international bodies, for example the European Commission, to develop a working definition of synthetic biology is relevant to the work of the Convention in this area and collaboration with these fora would avoid contradictions in the definition developed;

(e) A coordinated approach must be pursued between the Convention and its Protocols, in particular, but not limited to, ensuring a strong synergy between the programmes of work on risk assessment and risk management under the Cartagena Protocol and that on synthetic biology under the Convention. It must also be taken into account that the Nagoya Protocol also applies to conducting research and development on the genetic and/or biochemical composition of genetic resources, including the use of biotechnology as defined under Article 2 of the Convention;

(f) The creation of an online platform to facilitate the exchange of information on synthetic biology is noted as an important step towards providing all countries with access to information related to scientific, technical, environmental and legal issues, as well as capacity-building. A possible way forward in this regard is the establishment of a portal under the Biosafety-Clearing House where all Parties to the Convention – not only those that are also Parties to the Cartagena Protocol – could share information on the commercial release of organisms, components and products resulting from synthetic biology, as well as practical experience and guidance to facilitate capacity-building with regard to synthetic biology;

(g) Existing frameworks to assess the risks of LMOs can serve as a basis for the risk assessment of organisms developed through synthetic biology. However, there may be cases where specific guidelines to address the additional complexity and risks posed by synthetic biology organisms will be needed. As such, the current risk assessment framework must be reviewed and/or adapted, as appropriate, to address any gaps that may exist on how to assess organisms produced via synthetic biology, including how to approach the lack of adequate comparators in the risk assessment. When revising or adapting existing methodologies for risk assessment countries may take the following into account:

(i) Ensuring that risk assessment methodologies advance in parallel with progress in synthetic biology;

(ii) Structuring, standardizing and developing more effective mechanisms for the submission of relevant data on genetic modification and genetic elements to risk assessors;

(iii) Supporting the sharing of specific and relevant information on the components, equipment and systems used in the development process with the risk assessors;

(iv) Supporting the characterization of the biological function of the components and the development of computational tools that can predict the properties of the organisms containing such components;

(h) There is a need to develop an international framework to cover the organisms, components or products of synthetic biology techniques which also provides for an assessment of the cultural and socioeconomic impacts, primarily the impacts on small-scale farmers, and also on biodiversity, and in particular wild relatives;

(i) It would be helpful if all of existing regulatory frameworks were openly shared and discussed in relation to synthetic biology with best practise and gaps identified;

(j) More work is needed to understand how the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) and the Strategic Approach to Integrated Chemicals Management (SAICM), as well as international best practices, such as good laboratory practices (GLP) and good manufacturing practices (GMP), may apply to non-living components and products derived from synthetic biology techniques.

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AD HOC TECHNICAL EXPERT GROUP ON SYNTHETIC BIOLOGY
Montreal, Canada, 21-25 September 2015

ORGANIZATION OF WORK

Annotations to the provisional agenda

INTRODUCTION

1. In paragraph 4 of decision XII/24,[1] the Conference of the Parties to the Convention on Biological Diversity decided to establish an Ad Hoc Technical Expert Group (AHTEG) on Synthetic Biology, with terms of reference contained in the annex to the decision and attached below for ease of reference.

2. In paragraphs 5 and 6 of the same decision, the Conference of the Parties invited Parties, other Governments, relevant organizations, indigenous and local communities and relevant stakeholders to submit information to the relevant to the work of the AHTEG, as well as on measures undertaken in accordance with paragraph 3 of decision XII/24, including the identification of needs for guidance, and further information in response to paragraph 3(a) of decision XI/11.

3. Further, in paragraph 7 of the same decision, the Conference of the Parties requested the

(a) To make available the information submitted by Parties, other Governments, relevant organizations, indigenous and local communities and relevant stakeholders through the clearing-house mechanism of the Convention and other means;

(b) To convene a moderated open-ended online forum[2] to support the work of the AHTEG in meeting its terms of reference;

(c) To prepare an updated report on the work specified in paragraphs 3(a), 3(b) and 3(c) of decision XI/11, taking into account information submitted in paragraph 2 above and a synthesis of the outcomes of the process mentioned in (b) above and to submit these for consideration by the AHTEG;

(d) To submit for consideration by a meeting of the Subsidiary Body on Scientific, Technical and Technological Advice (SBSTTA) prior to the thirteenth meeting of the Conference of the Parties, the peer-reviewed reports of the outcomes of the process mentioned in paragraphs (b) and (c) above;

[1] Full text of the decision can be found at http://www.cbd.int/doc/decisions/cop-12/cop-12-dec-24-en.pdf.

[2] The open-ended online forum will be open to all interested participants and continue for a finite period of time.

4. In response to paragraphs 5, 6 and 7(a) of the decision, the sent out a notification inviting Parties, other Governments, relevant international organizations, indigenous and local communities and other relevant stakeholders to submit information on synthetic biology. A total of 30 submissions were received, among which were eighteen from Parties, one from a non-Party and eleven from organizations. The submissions were made available through the Biosafety-Clearing House.[3]

5. Further, in response to paragraph 7(b) of the decision, the invited the nomination of experts from Parties, other Governments, indigenous and local communities and relevant organizations to participate in the Open-ended Online Forum on Synthetic Biology and organized a series of moderated discussions from April to July 2015 in support of the work of the AHTEG.[4]

6. The also in response to paragraph 7(c) of the decision, prepared document UNEP/CBD/SYNBIO/AHTEG/2015/1/2 containing a report of the work done to date and analysis of the views expressed through the submissions in response to his notifications and to interventions made in Open-ended Online Forum.

7. In accordance with the elements of the decision, a face-to-face meeting of the AHTEG on Synthetic Biology is scheduled to take place in Montreal, Canada, from 21 to 25 September 2015.

8. Members of the AHTEG were selected in accordance with the consolidated modus operandi of SBSTTA[5] and decision XII/24, from among the nominations submitted by Parties taking into consideration geographical distribution and gender; and on the basis of their active participation in the Open-ended Online Forum and the approval of the SBSTTA Bureau. A limited number of experts nominated by other Governments and relevant organizations were also selected using the same criteria and approval process.

9. A report containing the results of the work of the AHTEG will be submitted for consideration by SBSTTA at its twentieth meeting, scheduled to be held in Montreal, Canada, from 25 to 29 April 2016 and made available through the CBD website and Biosafety Clearing House.

ITEM 1. OPENING OF THE MEETING

10. The of the Convention on Biological Diversity will open the meeting of the AHTEG on Synthetic Biology at 9:30 a.m. on Monday, 21 September 2015, followed by self introductions by the members of the AHTEG.

ITEM 2. ORGANIZATIONAL MATTERS

2.1. Election of officers

11. The members of the AHTEG will be invited to elect a Chairperson, or Chairpersons, and a Rapporteur for the meeting.

[3] The submissions of information on synthetic biology are available online at http://bch.cbd.int/synbio/notifications/.

[4] The discussions under the Open-ended Online Forum on Synthetic Biology are available at http://bch.cbd.int/synbio/open-ended/discussion.shtml.

[5] Annex III to decision VIII/10 of the Conference of the Parties, paragraph 18.

2.2. Adoption of the agenda

12. The AHTEG will be invited to consider and adopt its agenda on the basis of the provisional agenda prepared by the Executive Secretary (UNEP/CBD/SYNBIO/AHTEG/2015/1/1).

2.3. Organization of work

13. The AHTEG will be invited to consider and adopt the proposed organization of its work as contained in annex II to this document. The work will be conducted in plenary, with the establishment of working groups, as appropriate.

14. The meeting will be conducted in English only.

15. The working document and information documents prepared for the meeting are listed in annex III to this document.

ITEM 3. SUBSTANTIVE ISSUES

16. Under item 3, the issues set out in the terms of reference for the AHTEG will be considered.

17. After an introduction of the details of intersessional work to date by the Secretariat in support of the work of the AHTEG, the Group will be invited to consider the background document UNEP/CBD/SYNBIO/AHTEG/2015/1/2, as well as the submissions and interventions of the online discussions to assist it in its deliberations on each of the substantive items.

18. To support a common understanding and facilitate its deliberations on substantive issues, the AHTEG will be invited to refer to the term "components" (e.g. a naked DNA molecule) as parts used in a synthetic process, and that of "products" (e.g. a chemical fragrance) as the resulting output of a synthetic biology process, and to consider "components" and "products" as *non-living*.

3.1. Relationship between synthetic biology and biological diversity

19. In accordance with paragraph (a) of its terms of reference, the AHTEG will take note of the exchange of views on how to address the relationship between synthetic biology and biological diversity.

20. Synthetic biology falls within the scope of the broad definition of biotechnology under the Convention: "any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use".[6]

21. There are several applications where organisms, components and products of synthetic biology such as bioenergy, agriculture, pharmaceuticals and chemical production may interact with biological diversity. Such organisms, components and products of synthetic biology may have both positive and negative impacts on biological diversity at different levels, including genetic, species and ecosystems.

22. The AHTEG will be invited to structure its discussion on the relationship between synthetic biology and biological diversity in the context of the three objectives of the Convention, namely:

(a) The conservation of biological diversity;

(b) The sustainable use of the components of biological diversity;

[6] Article 2 of the Convention on Biological Diversity.

(c) The fair and equitable sharing of the benefits arising out of the utilization of genetic resources.

3.2. Similarities and differences between living modified organisms (as defined in the Cartagena Protocol) and organisms, components and products of synthetic biology techniques

23. In accordance with paragraph (b) of its terms of reference, the AHTEG will identify the similarities and differences between living modified organisms (LMOs; as defined in the Cartagena Protocol) and organisms, components and products of synthetic biology techniques to determine if living modified organisms derived from synthetic biology fall under the scope of the Cartagena Protocol.

24. Under the Cartagena Protocol on Biosafety, LMOs are defined as "any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology".

25. Furthermore, as per the Protocol, "modern biotechnology means the application of:

(a) In vitro nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles, or

(b) Fusion of cells beyond the taxonomic family,

that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection."

26. In its deliberations, the AHTEG will be invited to consider, on the basis of the definitions of the Cartagena Protocol, the similarities and differences between LMOs and the living organisms developed through current and predictable applications of synthetic biology, and between modern biotechnology and the different areas of synthetic biology, including DNA-based circuits, synthetic metabolic pathway engineering, genome-level engineering, protocell construction and xenobiology, with a view to identifying the extent to which organisms, components and products of synthetic biology techniques fall within the scope of the Cartagena Protocol.

3.3. Adequacy of other existing national, regional and/or international instruments to regulate the organisms, components or products derived from synthetic biology techniques

27. As per paragraph (c) of its terms of reference, the AHTEG will identify if other national, regional and/or international instruments adequately regulate the organisms, components or products derived from synthetic biology techniques in so far as they impact on the objectives of the Convention and its Protocols.

28. Building upon the discussion on item 3.2, the AHTEG will be invited to consider the existing national, regional and international instruments that regulate the organisms, components or products derived from synthetic biology techniques, and whether these instruments provide an adequate and comprehensive regulatory framework.

3.4. Towards an operational definition of synthetic biology comprising inclusion and exclusion criteria

29. As per paragraph (d) of its terms of reference, the AHTEG was mandated to work towards an operational definition of synthetic biology, comprising inclusion and exclusion criteria, using all relevant information, based on scientific and peer-reviewed studies.

30. Taking into account the elements set out in its terms of reference, as well as the views expressed in the submissions and online forum, the AHTEG will be invited to deliberate on the steps needed to move forward towards an operational definition of synthetic biology with a view to recommending a process to SBSTTA at its twentieth meeting.

31. In its deliberations on a process towards an operational definition that could assist Parties in their scientific assessments and decision-making, the AHTEG may wish to consider the following elements as a basis for the definition:

(a) Be based on scientific concepts;

(b) Be applicable to components, organisms and products of synthetic biology;

(c) Comprise measurable inclusion and exclusion criteria;

(d) Account for current and foreseeable technological developments of synthetic biology.

3.5. Potential benefits and risks of organisms, components and products arising from synthetic biology techniques to the conservation and sustainable use of biodiversity and related human health and socioeconomic impacts relevant to the mandate of the Convention and its Protocols

32. In accordance with paragraph (e) of its terms of reference, the AHTEG will identify the potential benefits and risks of organisms, components and products arising from synthetic biology techniques to the conservation and sustainable use of biodiversity and related human health and socioeconomic impacts relevant to the mandate of the Convention and its Protocols.

33. The AHTEG will be invited to consider, within the mandate of the Convention and its Protocols, the potential benefits and risks of synthetic biology techniques that were identified in the background documents, as well as in the submissions and interventions in the online discussions, and recommend whether or not they provide a comprehensive overview of the current state of knowledge.

3.6. Best practices on risk assessment and monitoring regimes currently used by Parties to the Convention and other Governments

34. As per paragraph (f) of its terms of reference, building on the work on risk assessment and risk management undertaken by the Cartagena Protocol, the AHTEG shall compile information on best practices on risk assessment and monitoring regimes currently used by Parties to the Convention and other Governments, including transboundary movement, to inform those who do not have national risk assessment or monitoring regimes, or are in the process of reviewing their current risk assessment or monitoring regimes and to help those Parties and other Governments to regulate organisms, components and products from synthetic biology techniques appropriately.

35. Taking into account the text and work on risk assessment and risk management of LMOs under the Cartagena Protocol, including its Articles 15 and 16 and annex III, as well as the "Guidance on Risk

Assessment of Living Modified Organisms" and "Training Manual on Risk Assessment of Living Modified Organisms, in addition to the examples and considerations of best practices on risk assessment and monitoring regimes that were submitted by Parties to the Convention and other Governments, the AHTEG will be invited to consider if additional efforts to compile information on best practices are needed, and to recommend a way forward with regard to facilitating the sharing, dissemination and use of this information by Parties and other Governments.

3.7. Degree to which the existing arrangements constitute a comprehensive framework in order to address impacts of organisms, components and products resulting from synthetic biology, in particular threats of significant reduction or loss of biological diversity

36. As per paragraph (g) of its terms of reference, the AHTEG will identify if the existing arrangements constitute a comprehensive framework in order to address impacts of organisms, components and products resulting from synthetic biology relevant to the objectives of the Convention on Biological Diversity and its Protocols, in particular threats of significant reduction or loss of biological diversity.

37. Taking into account the objectives of the Convention and its Protocols, and its deliberations on the other substantive items of the agenda, the AHTEG will be invited to discuss the extent to which arrangements that are currently in place, including but not limited to risk assessment principles and methodologies, provide an effective and comprehensive framework to evaluate, address and/or mitigate the potential negative impacts of synthetic biology on biological diversity.

ITEM4. CONCLUSIONS AND WAYS FORWARD, INCLUDING ELEMENTS TO FACILITATE FUTURE DISCUSSIONS AND ACTIONS ON SYNTHETIC BIOLOGY UNDER THE CONVENTION

38. In the light of the discussions under agenda item 3 above and taking into account the suggestions contained in document UNEP/CBD/SYNBIO/AHTEG/2015/1/2 regarding possible elements of a way forward, the members of the AHTEG will be invited to consider the general conclusions of their work and identify the core elements which they consider to be relevant to facilitate future discussions and actions on synthetic biology under the Convention.

ITEM 5. OTHER MATTERS

39. Under this item, participants will be invited to raise other matters relevant to the subject matter of the meeting.

ITEM 6. ADOPTION OF THE REPORT

40. The Group will be invited to consider and adopt its report, on the basis of a draft to be presented by the Rapporteur with the support of the Secretariat.

ITEM 7. CLOSURE OF THE MEETING

41. It is expected that the meeting of the Ad Hoc Technical Expert Group on Synthetic Biology will be closed by its Chairperson(s) in the afternoon of Friday, 25 September 2015.

Annex I

TERMS OF REFERENCE FOR THE AD HOC TECHNICAL EXPERT GROUP ON SYNTHETIC BIOLOGY

The Ad Hoc Technical Expert Group will include balanced representation of Parties from all regions and include representation of indigenous and local communities and all relevant stakeholders, including other Governments, with knowledge of the Convention and its Protocols,[7] and will report on its work to a meeting of the Subsidiary Body on Scientific, Technical and Technological Advice prior to the thirteenth meeting of the Conference of the Parties.

The Ad Hoc Technical Expert Group will:

(a) Take note of the exchange of views on how to address the relationship between synthetic biology and biological diversity;

(b) Identify the similarities and differences between living modified organisms (as defined in the Cartagena Protocol) and organisms, components and products of synthetic biology techniques to determine if living modified organisms derived from synthetic biology fall under the scope of the Cartagena Protocol;

(c) Identify if other national, regional and/or international instruments adequately regulate the organisms, components or products derived from synthetic biology techniques in so far as they impact on the objectives of the Convention and its Protocols;

(d) Work towards an operational definition of synthetic biology, comprising inclusion and exclusion criteria, using all relevant information, based on scientific and peer-reviewed studies;

(e) Identify the potential benefits and risks of organisms, components and products arising from synthetic biology techniques to the conservation and sustainable use of biodiversity and related human health and socioeconomic impacts relevant to the mandate of the Convention and its Protocols;

(f) Building on the work on risk assessment and risk management undertaken by the Cartagena Protocol, compile information on best practices on risk assessment and monitoring regimes currently used by Parties to the Convention and other Governments, including transboundary movement, to inform those who do not have national risk assessment or monitoring regimes, or are in the process of reviewing their current risk assessment or monitoring regimes and to help those Parties and other Governments to regulate organisms, components and products from synthetic biology techniques appropriately;

(g) Identify if the existing arrangements constitute a comprehensive framework in order to address impacts of organisms, components and products resulting from synthetic biology relevant to the objectives of the Convention on Biological Diversity and its Protocols, in particular threats of significant reduction or loss of biological diversity.

[7] The Ad Hoc Technical Expert Group will be convened in accordance with the *modus operandi* of the Subsidiary Body on Scientific, Technical and Technological Advice, except that there will be 5 to 8 experts nominated by each of the five regions.

Annex II

PROVISIONAL PROGRAMME OF WORK

Monday, 21 September 2015

9.30 a.m.	Opening of the meeting (agenda item 1)
Morning	Organizational matters (agenda item 2)
	Substantive issues (agenda item 3)
Afternoon	Relationship between synthetic biology and biological diversity (agenda item 3.1)

Tuesday, 22 September 2015

Morning	Similarities and differences between living modified organisms (as defined in the Cartagena Protocol) and organisms, components and products of synthetic biology techniques (agenda item 3.2)
Afternoon	Adequacy of other existing national, regional and/or international instruments to regulate the organisms, components or products derived from synthetic biology techniques (agenda item 3.3)

Wednesday, 23 September 2015

Morning	Towards an operational definition of synthetic biology comprising inclusion and exclusion criteria (agenda item 3.4)
Afternoon	Potential benefits and risks of organisms, components and products arising from synthetic biology techniques to the conservation and sustainable use of biodiversity and related human health and socioeconomic impacts relevant to the mandate of the Convention and its Protocols (agenda item 3.5)
	Best practices on risk assessment and monitoring regimes currently used by Parties to the Convention and other Governments (agenda item 3.6)

Thursday, 24 September 2015

Morning	Degree to which the existing arrangements constitute a comprehensive framework in order to address impacts of organisms, components and products resulting from synthetic biology, in particular threats of significant reduction or loss of biological diversity (agenda item 3.7)
Afternoon	Conclusions and ways forward, including elements to facilitate future discussions and actions on synthetic biology under the Convention (agenda item 4)

Friday, 25 September 2015

Morning	Conclusions and ways forward, including elements to facilitate future discussions and actions on synthetic biology under the Convention (agenda item 4) (*continued*)
Afternoon	Adoption of the report (agenda item 5)
	Other matters (agenda item 6)
5 p.m.	Closure of the meeting (agenda item 7)

Annex III

LIST OF DOCUMENTS FOR THE MEETING OF THE AD HOC TECHNICAL EXPERT GROUP ON SYNTHETIC BIOLOGY

Working documents

UNEP/CBD/SYNBIO/AHTEG/2015/1/1	Provisional agenda
UNEP/CBD/SYNBIO/AHTEG/2015/1/1/Add.1	Annotations to the provisional agenda
UNEP/CBD/SYNBIO/AHTEG/2015/1/2	Updated report and analysis of views in response to paragraph 7(b) of decision XII/24 on new and emerging issues: synthetic biology

Information and other background documents

http://bch.cbd.int/synbio/submissions	Submissions of views on synthetic biology by Parties, other Governments and organisations
http://bch.cbd.int/synbio/open-ended/discussion.shtml	Discussions under the Open-ended Online Forum on Synthetic Biology
https://www.cbd.int/doc/publications/cbd-ts-82-en.pdf	CBD Technical Series No. 82: Synthetic Biology
http://bch.cbd.int/protocol/text/	Text of the Cartagena Protocol on Biosafety
UNEP/CBD/BS/COP-MOP/6/13/Add.1	Guidance on Risk Assessment of Living Modified Organisms
UNEP/CBD/BS/COP-MOP/6/INF/12	Training Manual on Risk Assessment of Living Modified Organisms

14th INTERNATIONAL SYMPOSIUM ON THE BIOSAFETY OF GENETICALLY MODIFIED ORGANISMS (ISBGMO14)

(Guadalajara, Mexico, March 2017)

(version of 19 AUG 2015)

1. Composition of scientific programme committee

The composition of the programme committee is limited to 8 persons to ease the communication within the committee and to speed up the decision-making process.

ISBGMO14	Affiliation		Region
	EFSA	Public (governmental RA body)	IT
	Estel consult	Private	UK
	Pioneer	Private	US
	CIBIOGEM	Public (governmental RA body)	MX
	CERA-ILSI	Private	US
	Agroscope	Public (research institute)	CH
Jaimie Schnell	CFIA	Public (governmental RA body)	CA
	Cornell University	Public (research institute)	US

Contact details (eMails)

ISBGMO14	eMail
Jaimie Schnell	Jaimie.Schnell@inspection.gc.ca

2. Tentative list of themes for the symposium

2.1. General theme for the symposium

- ERAs for GM plants: past, present, future
- Using 30 years of knowledge on biosafety to build a better future
- Using 30 years of experience to further optimise ERAs of GMOs
- Learning from the past to improve future ERAs
- Applying 30 years of experience to the future
- Looking back 30 years, looking forward 30 years
- Others ...

2.2. Structure of the scientific programme

In the former ISBGMO symposium, the symposium lasted for 4 days, and consisted of a mix of 3 plenary sessions and 12 parallel sessions. The parallel sessions enabled to offer more diversity of relevant topics to address, thereby increasing the attractiveness/value of the symposium. In addition, 2 poster sessions and a pre-ISBGMO side meeting were held on specific topics. A possible outline for ISBGMO14 structure, based on that followed for ISBGMO13, is given below.

	Pre-ISBGMO	**Day 1**	**Day 2**	**Day 3**	**Day 4**
AM		Plenary session 1	Plenary session 2	Parallel sessions (3x*)	Parallel sessions (3x)
PM	Side meeting	Parallel sessions (3x)	Parallel sessions (3x)	FREE (social activity)	Plenary session 3
		Poster session I	Poster session II		

* Including a Pecha Kucha session dedicated to young researchers who would be offered the opportunity to briefly present their on-going research activities – http://www.pechakucha.org/faq

2.3. Plenary sessions (# 3): themes

- **Session 1:**
  - Looking back at / Taking stock of 30 years of experience on the safety assessment of GM plants to optimise/advance/simplify future ERAs
    - Problem formulation fit for purpose to optimise/focus ERA (general talk presenting problem formulation followed by concrete/real case studies)
    - Realised vs. hypothesised safety concerns (review of evidence and facts)
- **Session 2:**
  - ERA of GMOs – present
    - Global harmonisation of data requirements
      - While protection goals (or even data requirements) might differ across geographies due to legislation, social needs,

environment differences, some basic study concepts can be harmonised. For example, use of 20% as a limit for control mortality? Transparency in describing methods, results, analysis, etc. So build from a "can we agree on a ladybird beetle study design?" to a "can we agree on a trigger value to move between tiers" to a "can we agree on an acceptable end point" etc.

- Environmental risk management
  - Regulations, stewardship, measures, experiences (case studies: resolved and pending)
- Environmental risk communication

- **Session 3:**
  - ERA of GMOs – challenges ahead
  - ERA of GMOs in the face of global challenges (sustainability of ecosystems, food security, climate change, innovation)
  - Meeting global challenges – GM crops' role?
    - Proportionality of data requirements
    - New plant biotechnology-based breeding techniques
    - Synthetic biology
    - Gene drive technology

2.4. Parallel break-out sessions (# 9 to 12): themes

An important goal to achieve for the parallel sessions is to find a good balance between policy-oriented/conceptual talks and research talks (in which gathered data are presented). Research talks would then complement the policy-oriented/conceptual ones, and give more substance to the session.

Relevant topics	Why
First choice themes/topics	
Pecha Kucha session dedicated to young researchers/scientists (organiser tbc)	What about a pecha kucha session? These are 5-10 min talks run on a timed presentation that moves slides every minute. Presenters have to make their point in that time. This could be set up for students that may not yet have results, but have their research projects in place. They could tell us what they are doing in 10 minutes. They could even be associated with posters. We did some of these at Syngenta and they were fun, it is a dynamic way to learn what is going on without going into fine details Scientists, especially early-career researchers, are invited to present their finalised or on-going research. To help early-career researchers participate at ISBGMO14, ISBR could be offering a financial contribution to cover travel and

	accommodation costs of selected participants. We should therefore explore budgetary options, participation criteria, quality appraisal criteria, timelines for offer submissions and appraisal
Types of evidence and efforts necessary to inform the safety assessment of unintended changes/traits in GM plants (Jaimie)	This remains an unresolved issue in some jurisdictions, especially the EU, though there is little scientific evidence pointing to safety concerns. Perhaps it is time to reconsider/relax data requirements in the light of the weight of evidence accumulated over the last two decades. In this session, the pros and cons of OMICs could be discussed. It would also be relevant to discuss the relevance/proportionality of data requirements by comparing different plant breeding techniques I agree that this is an interesting topic. I just wonder whether this topic is highly relevant outside of Europe I was thinking that this discussion might not be limited only to unintended effects. I think the discussion could be generalised – for example, another topic that could be discussed is what you do when you have data gaps. I can envision scenarios where the mode of action has not been fully defined. Is knowledge about the MOA really critical to a safety decision? (how to cope with uncertainties/knowledge gaps in ERA; nice vs. need to know) At least for Mexico this topic is relevant and maybe for other Latin-American countries too. We agree that Jaimie could coordinate the session **Proposal**: Jaimie could be an excellent candidate to coordinate a dedicated break-out session on this matter. She wrote an excellent TRAG paper on this topic
Harmonisation and transportability of risk assessment data – criteria to assess the transportability of ERA data and to assess ERAs performed in other jurisdictions	A mix of science and regulatory. I like the idea of asking regulators why data isn't transported more. There has been some work done in South America on data transportability. Maybe (ILSI Argentina) would be willing to put something together. I think that a panel discussion might work? Or perhaps some small breakout groups in a workshop setting? could be an excellent candidate to coordinate a dedicated break-out session on this matter. Her TRAG paper is key

	Here I think it could be interesting to learn from risk assessors what restricts them in using data from other world regions Interesting topic that is generating a lot of discussion recently. Particularly regarding data from cultivating countries being accepted in importing countries. Hot topic in Japan where they considered what is done in Mexico, and are now changing requirements. Also the Brazilian bean case is a good example and some African countries are looking at this via COMESA We agree on having this topic, we recommend to join it together with the previews one, with a new name
Vertical gene flow between GM plants and wild/weedy relatives – dangerous liaisons or business as usual?	Vertical gene flow in maize remains a hot topic in Mexico. It would therefore be good to have a session on gene flow. Perhaps we could look at Canada with its long history with canola, then compare/contrast to other locations (Mexico) It would also be interesting to look at less domesticated more persistent/invasive plants (such as perennial plants, grasses and trees) We agree that the topic is important and particularly for centres of origin. We can coordinate a break-out session. We can identify some speakers with interesting papers. Since here there is an "ethic" component we could also explore the possibility to have a talk from the Nuffield Council Maybe we could here incorporate the recent sweetpotato story, http://www.pnas.org/content/112/18/5844 (note from ` – do we really want to consider horizontal gene flow?) This is a hot topic that keeps coming up in the discussions on the ERA guidance for the Cartagena Protocol, many countries are concerned about this type of gene flow in centres of origin. Mexico and maize, and Peru and potatoes could bring good topics One topic that could be discussed is "are there areas of the world where gene flow is not a problem?" For example, Japanese regulators regularly ask for detailed studies to show that imported maize won't become a weed in Japan. It seems that by now we should be at the point to put

	together a map showing where gene flow might be an issue to consider, and other areas where it just isn't **Proposal**: and/or could be excellent candidates to coordinate a dedicated break-out session on this matter
ERA considerations for RNAi-based GM plants – differences/similarities with GM plants expressing novel proteins (	This is quickly evolving field that will remain relevant over the years; it would be interesting to review finalised and on-going biosafety research activities in the field and review the gained knowledge. Perhaps knowledge gaps/research needs could be identified as well The topic needs to be addressed again. I would give it a high priority Yes, a good topic **Proposal**: could be an excellent candidate to coordinate a dedicated break-out session on this matter (like he successfully did for the previous ISBGMOs)
ERA considerations for GM insects	Release of organisms other than annual crop plants: apple, fish, mosquito, and others. Yes we could do just animals here and trees in the previous session I would like to put in a plug for a session on GE insects for pest and disease control. GE mosquitoes are being release in Brazil now and there is a petition to release them in Florida. As you can imagine, there is a bit of controversy about their deployment! at NC State was the Ent Soc America plenary speaker at the last national meeting and gave a good talk about the technology and of Oxitec, is receiving an innovation award for his work By the time of the meeting in March 2017, there will have been several trials and commercial projects involving release of GM insects. I think it would be a topic that we would be remiss if we did not include it in this conference. would be an excellent speaker on this topic While this is an interesting topic I wonder, whether ISBGMO will attract experts in this particular field. We could focus on GM insects and combine biosafety questions with

	questions about the efficacy of GM insects for pest control and their potential role in IPM I agree with – GM Insect Sessions in the past have been "what if" or hypothetical type sessions, by 2017 we should have several "and this is what happened" presentations There have been lots of new developments in this area, with field releases and new species. I think it would be interesting **Proposal**: could be an excellent candidate to coordinate a dedicated break-out session on GM insects (could serve as keynote speaker, Oxitec to offer a talk)
Ecosystem services concept in the frame ERA of GMOs	How do GM plants potentially affect ecosystem services, how to take ES into account when doing assessments for GM crops, etc. Basically – a practical/pragmatic discussion of GM crops and their benefits/risks rather than a theoretical discussion. And as part of this link in the IPM and "agro-ecosystem" idea We could also consider the use of the ES concept for the operationalisation of protection goals for use in ERAs of regulated stressors Important topic that could result in an interesting session. We should also include a discussion on whether the ES concept also covers the "intrinsic value of biodiversity" in a sufficient way Yes, a link with IPM and highlighting that ERAs for GM plants should consider the same ES as other agricultural products. Countries that have never worried about effects on NTOs of pesticides are suddenly concerned that they are not sure what NTOs to protect when GMOs are introduced it would be important to consider "sustainability" as a protection goal too. Here we could also have some links with the previous key presentation on Sustainable Intensification. I see many issues where GM crops can contribute (reduce pesticide use, reduce food waist [longer lasting fruits, etc.) adaptation to climate change) **Proposal**: Perhaps could follow this more closely (on-going EFSA

	activities in the frame of protection goals)
Tiered approach fit for purpose to inform the NTO risk assessment of GM plants	An interesting session would be that after 30 years I believe we have enough data to lock down the Tiered approach – that the lack of effects seen in lab studies have proven to be predictive of the lack of effects seen in the field I love this idea. Maybe we could use the session to discuss cases where it was claimed that field experiments/monitoring detected adverse effects not recognized in earlier, lower-tier studies **Proposal**: could be excellent candidates to coordinate a dedicated break-out session on this matter
Synthetic biology (organiser tbc)	I brought this topic up because I am current in the midst of a Cartegena Protocol – Ad Hoc Technical Committee discussion on the topic of SynBio and how it relates to the CP. If there is to be a discussion about ERA for SynBio organisms (and I think there will be), then I would rather see this discussion at ISBGMO rather than someone forming an entirely new group to talk about it. I suggested above that this might be an interesting presentation for the "future" plenary, however, I would rather see it presented in the middle of the meeting, possibly even as a. My reason is that some discussions of SynBio can be pretty distressing to some folks – the idea of entirely new organisms without "isolines" or entirely new gene constructs representing pieces of several different proteins – is new territory. At the same time, I believe that standard principles of risk assessment will work... problem formulation, exposure, hazard, etc. This topic has been suggested, it may be interesting for some countries as they are unsure on how to handle it. Also a working group is working on this under the Cartagena protocol and is generating unrest We agree that the ISBGMO is a good platform for discussing this issue. We could frame the discussion in terms of ERA being useful for assessing products of SB
ERA considerations for stacked events (synergism, subcombinations, segregating progeny, bridging studies) (organiser tbc)	This is a very hot topic in Mexico. We agree. There has been a lot of discussion in relation to stacked events occurring in landraces derived from gene flow. A question is whether the evaluation of a plant with 10

	transgenes will be the same that for a GMO with 3 genes? Perhaps here we could ask risk assessors and companies how they have addressed this issue in their assessments. Concrete case studies could be discussed here Again, this is a very hot topic in Europe. I'm not sure how relevant it is to the rest of the world Not so sure about this one, it is not an issue in many countries This topic is currently important in both Europe and Asia
Opportunities and ERA considerations pertaining to new GM plants (in terms of species (e.g., vegetables, trees, grasses), traits (e.g., output traits, drought/cold tolerance, use of genes coding for transcription factors) and new plant biotechnology-based breeding techniques (cisgenesis, genome editing, etc.) (organiser tbc)	This topic area will continue to grow in importance over the next couple of years so the timing will be good : Will modification of plants to address environmental stresses pose any risk to the environment? I believe that it would be useful to discuss ERAs for novel traits such as drought tolerance separately from the new breeding techniques. In my experience, discussions related to GM plants produced using new breeding techniques have always been very technical. I would prefer to stick to a discussion of traits This topic could give us an opportunity to have some public institutions talking about the products they are developing. The brinjal and LBR potato come to mind. Also a different product like pineapple. There is some research in Mexico on cisgenesis with maize also the apples in Switzerland? It would be good to have talks about the challenges that some of the new products pose, for example intractable proteins The challenge is to include the regulatory aspects. We consider that NPBTs could be a separate topic (Identified speakers (GM tres), drought tolerance maize)
ERA vs. ecological research – the relevance of a good problem formulation to ensure that gathered data are useful for ERA (organiser tbc)	: Perhaps it would be useful to have a dedicated session on problem formulation to introduce the concept once again. I realise this point has been extensively considered in previous ISBGMOs but given its importance it may be helpful to discuss it again, especially for those who are less familiar with ERA. The conceptual frame could be presented.

	Subsequently, concrete examples could be given in order to illustrate how a good problem formulation is constructed. Various areas of environmental concern could be considered, covering different species ×trait × intended uses combinations, and different levels of scientific uncertainties/familiarity
Second choice themes/topics	
Resistance evolution, management and monitoring – lessons learnt/moving toward integrated pest management (organiser tbc)	This will remain a relevant topic for discussion, though not everyone considers it a biosafety issues. Case studies for which the assumptions of the high dose/refuge strategy are met or not could be discussed. Concrete recommendations on how to improve IRM could be elaborated (pyramids, seed blends, crop rotation, etc.) I was always in favour of this topic. It is of high relevance in countries with large scale adoption I agree I am not a big IRM fan in terms of biosafety discussion – but could be persuaded to be less pessimistic if it was broadened to include "if resistance occurs, then what?" Meaning, an overall risk assessment of what happens as older control techniques need to be brought back into service to control the now resistant pests. One struggle I have with ISBGMO is that sometimes the sessions seem to look at only GM crops as if they were used by themselves and not as part of an overall agricultural system. So resistance in terms of overall agro-ecosystem risk assessment might be an interesting discussion We agree. We have to recognize that the GM crops are varieties and need to be managed as other agricultural varieties. We recently declared a region in the north of Mexico as "eradicated for the pink worm". Bt cotton played a roll along with IPM, this view could balance other cases where resistance has appeared faster (We hacve identify a couple of colleagues that could participate –weed)
How to increase trust in regulatory decision-making? (organiser tbc)	Will the use of the new technology promote less regulatory burden and enhance trust in the end user? How should we address the lack of trust by the public? This is important and could be combined with a discussion about trust in

	the technology
Proposals submitted by interested participants	xx
xx	xx
Third choice themes/topics	
Integrating the assessment of multiple stressors in ERA (organiser tbc)	This remains an important topic to explore. ERA currently does not consider simultaneous or sequential exposures to different regulated stressors that often happen when NTOs forage over a wide area. Instead, ERAs typically address specific stressors in isolation according to the relevant legislation. Therefore, it could be valuable to discuss how to test and/or assess multiple stressors. Perhaps useful tools could be discussed: (1) ecological/landscape modeling; (2) extrapolations from individual results to the population/community level; (3) revised bioassays; and (4) the use of an epidemiological approach to test the effects of multiple stressors to identify those stressors that have a significant interactive effect with other stressors. To discuss the type of actions required to move toward a multiple stressors ERA I agree to look into this issue, maybe it is somehow consider with a broader comparison when we do ERA, but not directly and explicitly assess
GM crops as part of agroecology (organiser tbc)	I seem to be seeing more discussion of Agroecology in different areas, for example, see attached from the Land Use Policy Group We are not sure about the concept. We suggest to join this topic with "Ecosystems services concept in the context of ERA of GMOs". We have also see this term in relation to sustainable intensification
Proposals submitted by interested participants	xx
xx	xx

3. Tentative list of topics deserving specific attention

The below tentative list of topics could be developed further as separate parallel break-out sessions.

- Biotechnology and ERA research in Mexico
- ERA considerations for GM trees – differences/similarities with "traditional" GM crops
- ERA considerations for other/new crops (e.g., vegetables) – differences/similarities with "traditional" GM crops
- ERA considerations for crops with output traits – differences/similarities with "traditional" GM crops
- ERA consideration for GM stacks
- Next generation of GMOs
- Opportunities and risk assessment/regulatory challenges pertaining to new plant biotechnology techniques
- Data quality of experimental studies supporting ERA of GM plants (covering both their usefulness (problem formulation; nice vs. need to know) and reliability (accuracy))
- ERA considered for endangered species
- Types of evidence and efforts necessary to inform the safety assessment of unintended changes/traits in GM plants
- Resistance evolution, management and monitoring
- IPM/IWM
- Ecosystem service concept to make protection goals operational (interactive exchange using case studies)
- How to account for scientific uncertainties in ERA and make them explicit?
- Value judgements in ERA – how much and what type of data are needed to make reliable risk conclusions?
- Post-market environmental monitoring
- Risk communication and perception
- Capacity building
- Regulatory decision-making (interplay between risk assessment and risk management, risk/benefits, weighing of policy objectives, what constitutes environmental harm)
- Systematic review approaches
- Ecological modelling
- Biological relevance
- Weighing costs and benefits
- Potential impacts of herbicide regimes associated with the cultivation of GM plants on farmland biodiversity
- Criteria to assess the transportability of ERA data and to assess ERAs performed in other jurisdictions

4. Candidate keynote speakers

4.1. First choice candidates

Name	Field of expertise	Comment
Topic: Global ecosystems, land use and the environmental implications of modern agriculture		
(Institute on the Environment (IonE); University of Minnesota; USA)		He was on our list for the past ISBGMO. He would be a good choice
Topic: Biodiversity and ecosystem processes (ecosystem services)		
(School of Natural Resources and Environment; University of Michigan; USA)		
Topic: Achieving food security for all in the foreseeable future: What will it take?		
University of Leeds; UK)		

	http://www.foodsecurity.ac.uk/	
NL)	Food and nutrition security, in historical perspective, utopia or dystopia?	
College of Human Ecology; Cornell University; USA)	The food system and its interaction with human health and nutrition; food and nutrition policy research; analyses of the impact of globalization on poverty, hunger and malnutrition in developing countries; ethical aspects of food policy; the political economy of food prices; and agricultural research and technology policy.	
Topic: Interplay between science, policy and decision-making		
(Consortium for Science, Policy & Outcomes; Arizona State University; USA)		

Topic: GM vegetables and their role in IPM and for food security (globally)		
(Department of Entomology; College of Agriculture and Life Sciences; Cornell University; USA)		would be good. I just wonder whether the keynote speaker should also be in the program committee
Topic: Bt crops and IPM		
(Department of Entomology; University of Minnesota; USA)		Not the most entertaining speaker
Topic: GM insect		
(Department of Entomology; NC State University; USA)		

Topic: Evolution, management and monitoring of resistance in insect pests (globally)		
(Department of Entomology; University of Arizona; USA)		
Topic: Progress made in ERA		
(Centre for Ecology and Hydrolog; UK)		

4.2. Second choice candidates

Name	Field of expertise	Comment
(Bio-Protection Research Centre; Lincoln University; New		is not the most entertaining speaker

Zealand)		

4.3. Third choice candidates

Name	Field of expertise	Comment
(Department of Zoology; University of Oxford; UK)		already gave a keynote talk at ISBGM013

4.4. Additional options to explore further

Name	Field of expertise	Comment
Various options	Integrated weed management and resistance evolution issues. *Proposal*: (USA); (AU); (USA); (USA); (USA); (USA)	
	Proposal: perhaps a big shot from Mexico	
	Proposal: perhaps a big shot with expertise on capacity building	
	Proposal: perhaps a big shot with expertise on risk communication	
proposals		

Status of Files

Synthetic Biology Working Group

A first meeting of the Synthetic Biology Working Group was held on November 7, 2013, and was attended by myself and Brian Colton. The working group was formed to support the work of the Synthetic Biology Steering Committee, on which Primal Silva and Cameron Duff sit. A workplan was discussed at the meeting. Current tasks include:

- Developing a Government of Canada working definition for Synthetic Biology. The Royal Society definition will be used as a starting point.
- Revise the paper developed by PHAC, *Oversight in Canada of Synthetic DNA: Issues and Options Analysis*. The first step in this task is to write summaries for revised sections in the Table of Contents.

I have volunteered to assist in writing summaries of the Table of Contents, but further guidance on accomplishing this has not yet been provided. A second meeting was scheduled for January 16, 2014, but was cancelled due to the departure of Rod Penney, the chair of the Working Group. A new chair, Dusan Valachovic, was recently identified and the next meeting of the Working Group has been scheduled for February 10. A teleconference is also being organized to discuss work on the Table of Contents revisions. Nicole's name has been put forward as my replacement to the Working Group.

- Working Group November 7, 2013 meeting minutes: RDIMS# 4481235
- Working Group Workplan: RDIMS# 4481295
- Synthetic Biology Definitions: RDIMS# 4481292
- PHAC *Oversight in Canada of Synthetic DNA* paper: RDIMS# 4481289
- Steering Committee June 20, 2013 meeting minutes: RDIMS# 4481286
- Steering Committee draft terms of reference: RDIMS# 4481282

Additional background documents shared by the working group can be found here:

O:\Science\Science Strategies\Science Advice & Biohazards\PBRA\Synthetic_biology

Status of Files – Jaimie – November 2015

Synthetic Biology

In the PBRA-Synthetic Biology folder (RDIMS# 6685434), you will find sub-folders containing my and Nicole's correspondence on this topic as well as sub-folders for the interdepartmental working group and the AHTEG on Synthetic Biology.

Interdepartmental Working Group

There has been very little interdepartmental activity of late. It should be noted that the interdepartmental working group changed its name to Oversight on Emerging Life Science Technologies. The lead of the working group is Kathrina Yambao at PHAC (kathrina.yambao@phac-aspc.gc.ca).

In August several members of the interdepartmental working group received a demarche request from on the topic of synthetic biology. Kathrina planned to engage the interdepartmental working group in preparing the response. Please see the email thread (RDIMS # 7419805) on this. Jim Louter shared a draft response from Risa Smith, who is engaged on the Convention on Biological Diversity front (RDIMS # 7419937). This document also contains the questions that were asked. Note that also received a similar request and she was interested in the GoC response in order to coordinate with

There are some materials shared by the interdepartmental working group housed here:

O:\Science\Science Strategies\Science Advice & Biohazards\PBRA\Synthetic_biology

Margaret Neuspiel (Office of the Chief Science Officer) has also been engaged with the interdepartmental working group. There are two spots for the CFIA on the working group – one to represent the plant business line and the other the animal business line. Margaret holds the latter spot. Any requests for input from the interdepartmental working group should be coordinated with Margaret.

AHTEG on Synthetic Biology

This past year there has been work done on Synthetic Biology under the Convention on Biological Diversity. You can find information on this at the following website:

https://bch.cbd.int/synbio

There were a series of online discussions from April to July on 7 topics. Following this, an Ad-Hoc Technical Expert Group on Synthetic Biology was formed and they convened in September. Jim Louter is representing the GoC. There may be some additional activity leading up to the 20th meeting of the SBSTTA in April/May 2016. We may be further engaged in this area either directly via Jim Louter or through the interdepartmental working group.

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s.19(1)

Date Oct. 29/2015

TTWG Conference Call

PBRA: Jamie, Andrea, Dylon, Cécile
APHIS:
PBO: Martin, John, " "
HC: Jennifer Holtzman, Jordan Bean
Mexico:
AFD:

1) Distribute excel table - Mexico
U.S. - non-regulated since last face-to-face
- Arctic Apple
- Dow 2,4-D, ε ?
- Simplot late blight
- MON 87411
- MON 87511 not recent
- 2 new branch chiefs -

I will send ←
- Memo - coordinated framework (Whitebook)
- how groups work together
- FDA, EPA, USDA
- request to update, develop long term strategy
- analyze future landscape for biotech
- series of public meetings
  - first is Oct. 31/2015
  - webinar, register in advance

Page

Date

- 2 more meetings in winter and spring
- outcome unclear still
- APHIS Biotech regulations (3-40) - update
  - withdrew rule to revise regs - 11/12/2008
  - each 3 public webinars - thinking on regs - 196 comments representing many ppl
  - current process good - time is right to revise
  - balance reg. oversight w risk - analysis first then regulate
  - proposed rule published by end of summer
  - notice of intent to publish....
  - drafting environmental assessment
  - trigger now is rDNA, plant pest
    - change to include additional organisms
  - incorporate noxious weed
    - develop WRA tool
    - using it to assess a grazing list of organisms
  - online regulatory status portal

Page

s.19(1)

Date

- challenges & hurdles

2) - enhance communication btw reg & industry
- U.S. - interested in guidance
  - love to see it if willing to share

3) - Mexico proposes to plan a seminar on bioinformatics
  - using it for pathogen characterization
  - applicable to GMOs as well.
  - database development aspects
  - shared platforms btw countries for GMO organisms sequence data
  - Cartagena Protocol?
  - shared molecular variants detected or proposed.

BI?

- CBI, may be difficult
- don't own info - may or may not be CBI
- have to think - interest in discussing
- see proposal on merits
- once de-regulated, goes public

- Mexico - will draft proposal w additional info.
- currently working on infrastructure, capacity building

Date

- Mexico - interested in seminars on CRISPR
- U.S. - at least 2 seminars to be shared in current workplan.
- BRS - possible seminar - development of improved alfalfa - Professor Dexon
- 2 webinars in ~~oct~~ Nov. 5 - gene drives
  Nov. 19 -
  RA and biosecurity considerations
- 2 recorded webinars on this topic as well

4) Global & LLP initiative (GLI)
- Feb. 2016 - FAO - Symposium on Biotech
- have GLI on margins of Symposium in Rome
- may be conflicts
- Mexico to share position in near future

OECD in April - WG & TF
- NBT in between

6) Canada to lead next call
Late January - 25 to 29th.

Face-to-face - hosted by Canada in May
US. - ~~May~~ last week (May 23) - no good.
Mexico - domestic consultations and will return an answer

[redacted]

Date

2 Impact scenarios — Low 1/10 yrs
High 1/20 yrs

Confined field trial non-compliance

~~what in US~~
Flax

Moderate
U.S wheat

Assumptions document
→ Jaime to start.

Lynn Stewart

Page

Crispr
Database - Karen ?
Giant ragweed
1651 - Karen?
1666?

Date

IRMF - Scoring - 59-1F-220.

Sale of non-certified seed?
All PNTs certified?

Certified seed = terminal pedigreed class

Acres → Amt of seed → Price of seed →
Direct conversion? What about grain?
→ avg by crop ok?
TOTAL VALUE

Do we need value of all seed sales in that window? Might be a good check even if we don't

How do we do corn? Do we want a consistent approach?

Corn - external database

Pre-market - will capture farm gate value
↳ not any further down the chain eg. crushing

Page

[redacted]

From: Jaimie Schnell
Date: 2014-01-16
Time: 1:00 PM - 3:00 PM
Subject: Synthetic Biology Working Group Meeting
Place: 8 Colonnade Rd, Room 103

From: Jaimie Schnell
To: Jaimie Schnell; van der Lee, Nicole
Date: 2014-01-16
Time: 1:00 PM - 3:00 PM
Subject: Synthetic Biology Working Group meeting
Place: 8 Colonnade Rd, Room 103

Hi Nicole,

Here is an appointment for the other meeting I mentioned to you. The Synthetic Biology Working Group was just recently formed. This is only our second meeting. I haven't yet seen an agenda for the meeting, but I'll be sure to share it with you once I receive it. I hope you can make it!

Jaimie

From: **Jaimie Schnell**
Sent: **2014-01-23 2:25:36 PM**
To: **dusan.valachovic@phac-aspc.gc.ca**
CC: **Nicole.vanderLee@inspection.gc.ca;kirsten.jacobsen@phac-aspc.gc.ca**
BCC:
Subject: **Re: Introducing Dusan Valachovic**

Hi Dusan,

I did agree to assist in drafting the outline, but I'm actually at the end of this week. Nicole van der Lee will be replacing me, and she'll be in touch with respect to her availability for the meeting in February. It may be a few weeks before Nicole officially replaces me on a full time basis, so depending on the timing of the work on the outline, she may or may not be able to assist. When the work gets underway, please contact Nicole and she'll be able to let you know if she can take on the work.

Regards,
Jaimie

Jaimie Schnell
Risk Assessor - Biotechnology | Évaluatrice des risques - biotechnologie
Plant and Biotechnology Risk Assessment Unit | Unité d'évaluation des risques des végétaux et des produits de la biotechnologie
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Government of Canada | Gouvernement du Canada
>>> Kirsten Jacobsen <kirsten.jacobsen@phac-aspc.gc.ca> 2014-01-23 12:47 PM >>>
Good afternoon,

I would like to take this opportunity to introduce Dusan Valachovic to you. Dusan is replacing Rod on the synthetic biology project at the Public Health Agency of Canada for the next several months, and will also take his place on the Working Group in support of the Steering Committee. He just started with us this week, but has already gotten fairly up to speed.

In the next few days, Dusan will be in touch with those of you who agreed to assist in drafting the outline for the re-write of the paper on the Oversight of Synthetic Biology Research. Please correct me if I am mistaken, but I believe Jamie Shcnell (CFIA), Jean-Philippe Lacosse (Public Safety), and Les Nagata (DRDC) had offered to assist.

In addition, I would like to re-schedule the next working group meeting for early February. Can you let Dusan and me know your availability for the week of February 10?

Thank you,

Kirsten

Kirsten Jacobsen, Ph.D.
Centre for Biosecurity / Centre de la Biosûreté
Public Health Agency of Canada / Agence de la santé publique du Canada
8 Colonnade Road, room 3018 / 8 chemin Colonnade, pièce 3018
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<<File: TEXT.htm>>

s.19(1)

From: Philip Macdonald
To: Cindy Pearson
Date: 2014-05-01 11:58 AM
Subject: Fwd: BBSRC workshop on new crop breeding technologies, 19 June - invitation to speak

As requested.

>>> 2014-04-28 11:15 AM >>>
Philip Macdonald, Canadian Food Inspection Agency

Dear Mr Macdonald

I am writing from the (UK) Biotechnology and Biological Sciences Research Council (BBSRC),

to ask if you (or an appropriate colleague) would be prepared to give a short talk for us at a BBSRC workshop on New Crop Breeding Technologies, to be held at the Royal Society, London on Thursday 19 June 2014. of the UK Government's Advisory Committee on Releases to the Environment (ACRE), suggested it would be valuable to hear a perspective from the Canadian Food Inspection Agency at this workshop.

The aim of the workshop is to bring together relevant experts from a variety of backgrounds to discuss current and prospective developments in new genetic technologies, their application in crop breeding and implications for risk assessment and regulation. The workshop is intended as a step towards developing a position statement (from BBSRC, potentially with other organisations) on new crop breeding technologies.

The technologies in question would include molecular genetic techniques for genome editing (site-directed mutagenesis, such as CRISPR, TALENs, ZFN technologies, oligo-directed gene targeting) and tools for epigenetic modification (such as RNA-dependent DNA methylation for gene silencing). The workshop and position statement are not intended to focus primarily on 'traditional' GM (transgenics etc) although clearly this is part of the context. We are placing the emphasis on crops, while recognising that many of the same techniques and regulatory issues will also be applicable in farmed animal and other systems.

A series of short talks is intended help to set the scene and provide a shared understanding for those with different backgrounds and areas of expertise. They will form the basis for structured discussion sessions that will identify the main issues and potential ways forward, which can then feed into the position statement.

If you would be available and willing to speak, we would like your talk to outline the position on risk assessment and challenges in relation to these new technologies (and potentially others in the future), from the perspective of the Canadian Food Inspection Agency. We suggest your talk should be for 10 minutes plus time for one or two immediate questions. We would of course also welcome your input to the discussions throughout the day. However, if it is not feasible to arrange travel to the UK for this meeting, we would be happy to explore options for delivering a talk by video link.

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I would be grateful if you could confirm as soon as possible whether or not you are able to attend and speak at the workshop. I would be happy to discuss the workshop with you if you have any queries. If you are unable to accept this invitation, we would greatly appreciate your suggestions for alternative speakers who may be able to provide a perspective from the Canadian Food Inspection Agency.

I look forward to hearing from you.

Best regards,

Biotechnology and Biological Sciences Research Council (BBSRC),
Polaris House, North Star Avenue, Swindon SN2 1UH
> tel
www.bbsrc.ac.uk<http://www.bbsrc.ac.uk>

BBSRC - 20 Years of Pioneering Great British Bioscience.
www.bbsrc.ac.uk/twenty<http://www.bbsrc.ac.uk/twenty>

Cindy Pearson - For Comment: Oversight of Emerging Life Sciences Technologies (Formally Synthetic Biology)- Briefing Note and Appendices

From: Nicole van der Lee
To: Davis, Sarah G.; Duff, Cameron; Esber, Paula; Kehoe, Amy; Macdonald,...
Date: 2014-05-01 7:22 PM
Subject: For Comment: Oversight of Emerging Life Sciences Technologies (Formally Synthetic Biology)- Briefing Note and Appendices
Attachments: CFIA_ACIA_-_#5320891_-_vR_-_PBRA-_Synthetic_Biology-_Draft_Memo_to_Deputy_Minister.DOCX.DRF; CFIA_ACIA_-_#5320914_-_vR_-_PBRA-_Synthetic_Biology_Steering_Committee_and_Working_Group_Member_List.XLSX.DRF; CFIA_ACIA_-_#5320942_-_vR_-_PBRA-_Steering_Committee_for_the_Oversight_of_Emerging_Life_Science_Technologies_Terms_of_Reference.DOCX.DRF; CFIA_ACIA_-_#5320967_-_vR_-_PBRA-_Synthetic_Biology-_Proposed_Outline_for_Revised_Options_Paper.PPT.DRF; CFIA_ACIA_-_#5320987_-_vR_-_PBRA-_Synthetic_Biology_-_Definition_and_Scoping_Exercise.PPT.DRF; CFIA_ACIA_-_#5320997_-_vR_-_PBRA-_Synthetic_Biology_Steering_Committee_and_Working_Group_Activities_and_Resources.XLSX.DRF

Hello Everyone,

The email below was sent out by the Chair of the Working Group for the Oversight of Emerging Life Science Technologies (formerly Synthetic Biology Working Group). The email requests that comments are provided on behalf of each working group members department/agency on the attached documents. As such, PBRA is happy to offer to compile and roll-up comments on behalf of the CFIA. It is also important to note that in addition to comments they are requesting that resources be identified (including human resource and/or financial cost) to assist with the completion of a revised options paper.

At this time we are sending the documents out for comment to the steering committee and working group representatives from the CFIA, as well as Plant Health Research and Strategies and the Plant Biosafety Office. If we have missed any groups/individuals that you think should be involved, please contact me and I will ensure to forward this message along to them.

In terms of time lines, they are looking for comments by mid-May, thus I would appreciate it if I could receive **comments back by May 9th**. For convenience, I have saved all the documents in RDIMS so that comments can be input directly into the files.

Should you have any questions please feel free to contact me.

Thank you,
Nicole

Nicole van der Lee, M.Biotech.
Risk Assessor - Biotechnology | Évaluatrice des risques - biotechnologie
Plant and Biotechnology Risk Assessment Unit | Unité d'évaluation des risques des végétaux et des produits de la biotechnologie
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Government of Canada | Gouvernement du Canada

>>> Dusan Valachovic <dusan.valachovic@phac-aspc.gc.ca> 2014-04-29 10:11 AM >>>
Dear Working Group members;

As you will have seen from the minutes from the last Steering Committee meeting, we have been asked to prepare a joint briefing note that will be

routed to respective Deputy Ministers. The BN will provide an overview of our activities to date and seek approval of the plan, including resources needed for its completion.

Attached are draft memo and appendices - please send us your comments by May 16th so we can update the draft. We will then leave it up to each of you to refine and start the process to route the BN to your respective Deputy Ministers.

As noted, the Steering Committee asked that the BN include an estimate of the resources that will be required to draft the options paper. Could you please take a look at the Appendix E (Outline deck) and identify areas of the paper where your department/agency will be able to contribute and estimate the human resources costs (or financial if you think there will be expenses to incur). PHAC can lead the group work on the majority of the paper; however, we propose that Jamie Flammenbaum be the lead on the ethical considerations and Andrew Halliday be the lead on the international context. If your department or agency should be the lead on any of the remaining content, please put your name forward.

Updating the assessment is the real research component and will likely be the most resource intensive. PHAC can lead this work, but it will be important to have other working group members participate in this research, so please put your name forward if you can contribute.

Thank you.

Dusan Valachovic
Policy Analyst
Centre for Biosecurity / Centre de la Biosûreté
Public Health Agency of Canada / Agence de la santé publique du Canada
100 Colonnade Road, room 1007-48 / 100 chemin Colonnade, pièce 1007-48
Ottawa

ADM letterhead

FOR INFORMATION

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Classification (if applicable)

MEMORANDUM TO THE DEPUTY MINISTER AND THE ASSOCIATE DEPUTY MINISTER OF HEALTH (or XXX)

Oversight of Emerging Life Sciences Technologies

SUMMARY

- The Public Health Agency of Canada (PHAC) co-chairs an interdepartmental Steering Committee (SC), looking at the oversight of emerging life sciences technologies, and particularly synthetic biology.
- The SC includes representatives from 13 departments and agencies and is supported by a Working Group (WG) who will be conducting an options analysis to inform the SC on developments in emerging life sciences technologies and prepare recommendations for key actions that the Government of Canada could take to mitigate the risks associated with emerging technologies
- This briefing will provide an overview of the SC and WG activities to date, and outline the next steps in examining this complex issue.

BACKGROUND

New and emerging technologies in life sciences, especially in synthetic biology, are developing rapidly and have made numerous advancements in recent years. A key indicator was the 2010 creation of a bacterium with a completely synthetic genome by researchers at the J. Craig Venter institute. Since then, a group of researchers published the first-ever successful synthesis of a functional designer eukaryotic chromosome (March 2014), another significant leap in synthetic biology.

As the field has advanced, access to the technologies that enable emerging sciences such as synthetic biology has become more and more accessible and affordable. The international community has had several recent opportunities to observe the potential risks associated with emerging life sciences technologies. These include the risks

associated with intentional misuse (dual use) as well as the unintended consequences of such research (e.g., accidents, unpredicted interactions).

One of the most salient examples occurred in 2011 when two research teams generated mammalian transmissible lab strains of H5N1. In 2013, the same researchers announced their intent to conduct similar studies with the H7N9 flu virus that is currently spreading in China and neighbouring countries. These studies prompted international debate about research with the potential for dual use, including how risks are weighed against the potential benefits, and how the details of such experiments are shared with the world.

The increase in accessibility has also broadened the landscape in terms of who is conducting emerging life sciences research. The international genetically engineered machines (iGEM) competition, for example, provides high school and university students with a kit of biological parts that they use to design and build new biological systems using synthetic biology. There is also a significant increase in activity amongst DIY biologists and citizen scientists, many of whom may have little or no scientific training.

The growing number of examples of emerging life sciences research prompted an interdepartmental dialogue on the oversight of such technologies, starting with the existing federal legislative framework. While the current framework provides quite robust oversight over the products of emerging life sciences technologies (e.g., pathogens, products aimed at environmental remediation, food or drug additives), there are still many unknowns. Likewise, there is uncertainty as to the degree of oversight along the research spectrum, from planning to publication. In order to examine this issue more closely, an Interdepartmental Steering Committee, supported by a Working Group, was established. The principle objective of the committee will be to develop recommendations for key actions the Government of Canada could take to address the risks associated with emerging life sciences technologies. See Appendix A for the Steering Committee and Working Group members and Appendix B for the Terms of Reference for the Steering Committee.

To date, the Steering Committee and Working Group have each met twice. An outline for an options analysis to inform the development of recommendations for key risk mitigation actions has been drafted (Appendix C), and the Committee has settled on a working definition of synthetic biology and scope of the scientific activities that will be considered by the Committee as emerging life sciences technologies of interest (Appendix D).

CONSIDERATIONS

The Steering Committee anticipates engaging experts from private sector and academia, as well as public groups, to gather information on existing oversight mechanisms related synthetic biology research, and the production, sale, and use of enabling technologies.

PORTFOLIO CONSIDERATIONS

All departments/agencies represented on the Steering Committee and Working Group will work within their respective mandates and responsibilities to support the

development of an options paper and recommendations for the path forward. The Public Health Agency of Canada will continue to act as the secretariat, coordinating meetings and the development of the options paper. In order to develop recommendations for the Government of Canada, targeted research will be necessary, and will require the commitment of finite human resources for implicated departments and agencies. An estimate of the time necessary to complete the options paper and recommendations is detailed in Appendix E.

NEXT STEPS

The Working Group, with input and direction from the Steering Committee, will conduct targeted research and draft an options paper on the oversight of emerging life sciences technologies in Canada. This will be used to inform key recommendations for the Government of Canada that could be implemented to mitigate the risks associated with this advancing field, including key Government of Canada players. Once drafted, a Government of Canada framework will be developed, detailing the approach being taking to mitigate these risks.

RECOMMENDATIONS/CONCLUSIONS

It is recommended that the Deputy Minister approve the proposed plan to draft an options paper and key recommendations, including the implicated resources. Once complete, the Deputy Minister will be briefed again on the progress and research outcomes, and will be presented with the draft recommendations from the Steering Committee.

Steering Committee for the Oversight of Emerging Life Science Technologies

Draft Terms of Reference

The Steering Committee for the Oversight of Emerging Life Sciences Technologies was established in June of 2013 in response to the identification of the need to provide federal government oversight for the rapidly evolving life sciences technologies, such as synthetic biology.

Mandate:

The complexity of emerging life sciences technologies, such as synthetic biology, necessitates the establishment of an expert advisory committee that will give advice and make recommendations respecting the development and implementation of a proposed framework for the oversight of emerging life sciences technologies in Canada. Public Health Agency of Canada (PHAC) will co-chair the Steering Committee for the Oversight of Emerging Life Sciences Technologies (hereafter, **the SC**) with a second co-chair to be determined. In the interim, the co-chair will be selected on a rotating basis. The SC will work strategically and cooperatively to address the residual risks associated with emerging life sciences technologies.

The SC will provide a forum for communication, consultation and coordination between the federal government departments or agencies that deal with issues surrounding emerging life sciences technologies as part of their mandate. The purpose of the Committee is to propose a forward plan that will allow the Government of Canada to contribute to the mitigation of the risks associated with advancements in emerging life sciences research, such as synthetic biology, while recognizing the benefits that may accrue from its use.

Specifically, the committee will:

- Utilize an interdepartmental approach to advise on the development and implementation of a proposed emerging life sciences oversight framework

- develop strategies that deal with emerging life sciences issues such as research with dual use potential, biosecurity and biosafety;
- recommend the establishment of sub-committee's or working groups that will meet separately to discuss specific emerging life sciences related issues;
- provide recommendations based on reports provided by the Working Group based on their review and consideration of the latest research publications in emerging life sciences technologies, such as synthetic biology;
- review and consider international trends and developments in emerging life sciences, such as synthetic biology.

Guiding Principles:

The Committee will operate in a manner consistent with the following guiding principles:

- the safety of Canadians, animals, and the environment is paramount, in consideration of the risk management framework;
- the values of Canadians will be considered when proposing oversight activities for emerging life sciences technologies;
- the responsibility to carry out follow-up actions identified in the Government of Canada framework will be shared, within the respective mandates of departments and agencies;
- a variety of risk mitigation tools will be considered in order to maximize impact while still fostering scientific research and innovation;
- the benefits, as well as the safety, security, and ethical issues and challenges associated with emerging life sciences technologies research will be considered when developing the framework;
- all activities undertaken as a result of discussions of this committee will be done in an open and transparent manner;
- an evidence-based approach will be used;
- existing and future international obligations stemming from conventions and agreements will be respected.

Committee Structure and Operations:
The Committee will be co-chaired by the Director General of the Centre for Biosecurity, PHAC and one other co-chair to be identified. PHAC will provide secretariat services to the committee.

The co-chairs will serve as facilitators of the Committee meetings. Duties will include convening and managing meetings and conference calls, preparing agendas and confirming consensus decisions. Proceedings of the meetings will be provided to all Committee members.

The Committee will follow a consensus based decision making process. Membership is by invitation extended, but not limited to, the following:

- 1 representative from Agriculture and Agri-Food Canada (AAFC)
- 2 representatives from the Canadian Food Inspection Agency (CFIA)
- 3 representatives from Health Canada (HC)
- 1 representative from the Canadian Institutes of Health Research (CIHR)
- 1 representative from Environment Canada (EC)
- 1 representative from Department of Foreign Affairs, Trade and Development (DFATD)
- 1 representative from the National Research Council (NRC)
- 1 representative from the Natural Sciences and Engineering Research Council (NSERC)
- 2 representatives from the Public Health Agency of Canada (PHAC)
- 1 representative from Public Safety and Emergency Preparedness Canada (PSEPC)
- 1 representative from Industry Canada
- 1 representative from the Department of National Defence

Invitation may also be extended by the Co-Chairs of the Committee to other individuals to be observers at Committee meetings.

Additional expertise on specific areas relating to emerging life sciences technologies, such as synthetic biology, may be required and invited to provide presentations or advice to the Committee on an as needed basis.

Meetings

The Committee will meet two times per year. Additional meetings, if required, will be at the call of the Co-Chairs, and can take place either in person, by videoconference or by conference call.

Budget and Financial Matters:

Each representative will be responsible for his/her own direct costs associated with participation, including travel, conference calls and accommodation. Other direct meeting costs will be assumed by PHAC.

Oversight of Emerging Life Sciences and Technology

Proposed Outline for Revised Options Paper

Rewrite of the Options Paper

- The Science Advisory Board recommended that the 2011 Issues and Options paper be rewritten to include
  - A "case-study approach" to really highlight the issue
  - A clear definition of "synthetic biology", and a clear scope that would exclude what is already robustly covered, such as site-specific mutagenesis
  - An outline of the questions that still need to be answered
- Structure of the Document
  - Founded on original options paper with additional research, clear objectives/outcomes
  - Include recommendations that can be tied to specific actions to inform the development of a long-term action plan

Audience

- Core Audiences
  - Steering Committee,
  - Department and Agency Senior Executive Committees (for information or for approval),
  - Science Advisory Board
- Needs to capture expectations of all departments/agencies
- Lead to the development of an action plan that will allow the identification of department/agency roles and responsibilities
- Steering Committee members to identify other audiences for the paper

Defining the Issue

- Potential benefits of emerging science and technology, such as synthetic biology
- Is there a real risk? (Crisp narrative)
  - Yes and Why
  - Implications
  - Real examples relevant to broad range of applications of emerging biological science and technology, such as synthetic biology research
- Risk Statement:
  - The current legislative/regulatory framework may not be comprehensive enough or sufficiently evolved to address oversight of emerging biological science and technology
- Ethical considerations – (high level summary, but will also be addressed through document)
  - Newfield Council report as 'gold standard'
  - Summarize key points from this and other documents
  - Even if technology itself is not harmful, there might be ethical boundaries
  - Who makes decision – government, researchers, public?
- How to address development of a framework for the oversight of emerging biological science and technology
  - Existing regulations and guidelines that address emerging biological sciences (for exclusion from scope)

Objective

- To develop a Canada-wide approach for addressing risks associated with emerging biological science and technology, such as synthetic biology (Framework)
  - Clear definition of the scope of the paper (loosely based on definition of Synthetic Biology)
  - Examples of what is "in scope" and what is "out of scope", including exclusion of emerging biological science and technology that is robustly overseen by existing regulation or guidance
  - Clear distinction between dual-use and unintended consequences

Updated Assessment of Existing Oversight

- Research Component
  - What do we want to achieve
  - Who are the players
  - What are the vehicles
  - What are the specific outcomes
  - Gap analysis

International Context

- Overview
  - » We have to focus on Canada, but our solution can't be completely opposed to international context – our approach will impact international interactions
- Parallels with other sciences – similar to chemical engineering, GMO, nanotechnology
  - » Lessons learned
- Current international conventions might not be sufficiently evolved to address emerging biological science and technology - possible gap with respect to existing models because linked to "organisms"
  - » International frameworks (e.g., , Biological Toxins Weapon Convention, Australia Group)

Recommendations

- Identify key actions that could be taken to address gaps
  - » The paper will include greater detail than the 2011 paper that can feed into specific actions
- Leverage intergovernmental committees to answer certain research questions
  - » Issue of timing with this approach
- Elaborate on private sector engagement – identify key players in industry and contact them (technology manufacturers, synthesizers, brokers, etc.)
- Elaborate on experts from academia to assist in specific research
- Question for Steering Committee about desired products of this research
  - » Options paper with recommendations (paper re-write)
  - » Framework for addressing issues and gaps?
  - » Government of Canada action plan with accountable leads?

Considerations and Questions

- Does this Outline capture what should be captured?
  - » What is missing?
  - » What should be emphasized?
- Is there a commitment to allow Working Group members to participate in the writing of the Options paper?
  - » Human Resource implications
- Other comments or questions?

Synthetic Biology – Definition and Scoping Exercise

Proposed Scope Definition: "Emerging Life Sciences and Technology"

Public Health Agency of Canada / Agence de la santé publique du Canada

Canada

Defining Synthetic Biology

- One of the core recommendations of both the Science Advisory Board and the Synthetic Biology Steering Committee was to clearly define synthetic biology in order to frame the issue
- The Working Group began by examining the numerous existing definitions. In general, there is consistency between existing definitions.
- Synthetic Biology was defined in the initial options paper (July 11, 2011)
  - » **Synthetic Biology** is a developing interdisciplinary field that focuses on the design and fabrication of novel biological components and systems as well as the redesign and fabrication of existing biological systems.
- The Working Group proposed that the Royal Society definition be adopted as a simple and clear definition of Synthetic Biology
  - » **Synthetic biology** involves the design and construction of novel artificial biological pathways, organisms and devices or the redesign of existing natural biological systems.
- Key challenge with all definitions is that they exclude studies that are based on emerging technologies and have significant dual-use potential (e.g., reconstruction of 1918 Spanish Flu, Engineered mammalian transmissible H5N1)

Scope of Steering Committee and Working Group Activities

- At the June 20th Steering Committee meeting, the need to look broader than synthetic biology and consider the issue of emerging technologies as a whole was identified.
  - » Caveat that the issue of emerging technologies have an inherent level of uncertainty
- The following scope is proposed (adapted from the Royal Society Definition)
  - » **Emerging Life Sciences Technology (e.g., synthetic biology)**
    - **Emerging Life Sciences Technologies, such as synthetic biology,** are biological sciences that involve the design and construction of novel artificial biological pathways, organism, and devices; or the redesign or reconstruction of natural biological systems.
    - The work to address the oversight of emerging life sciences technologies will not cover any relevant areas of biological sciences that are already adequately overseen by existing frameworks or guidelines.
- The scope will be supported by growing list of in- and out of-scope examples

Examples of Endeavours that would be "In Scope"

- Experiments that increase pathogen risk by modifying the inherent characteristics of the pathogen (pathogenicity, communicability, host range, susceptibility), for example
  - » Altering the mode of transmission and host range such as in the mammalian transmissible H5N1 studies and planned studies on H7N9
  - » Addition of antibiotic resistance genes into wild-type bacteria
  - » Incorporation of interleukin-4 gene in mousepox, which resulted in a virus with increased virulence due to suppression of T-cell cytolytic response to the virus.
- Experiments that upregulate or supress functions (genes, for example) of systems with clear potential for dual-use applications or high potential for unintended consequences
  - » Example from nature – Atlantic killifish exposed to polluted water have evolved a mechanisms to shut off the genetic pathway that leads to PCB poisoning – while not an experimentally created system, the possible application to other species could be attractive, and any intentional release could have high potential for unintended consequences.
- Creation of new life through genetic engineering
  - » Creation of "mycoplasma laboratorium" – Venter institute
  - » Creation of a novel infectious prion or prion-like agent
- Reconstruction of existing or extinct organisms from synthetic nucleotides
  - » 1918 Spanish flu, small pox, polio virus
- Biological sciences that make use of "biobricks"

Examples of Endeavours that would be "Out of Scope"

- Non-biological emerging technologies, such as nanotechnology or nuclear technology
- Biological technologies that are adequately covered by other guidelines
  - » Example: creation of stem cells from adult precursors through the use of non-genetic engineering techniques;
    - Stem cell research in Canada is governed by the *Tri-Council Statement: Ethical Conduct for Research Involving Humans* (TCPS), the *Assisted Human Reproduction Act* (2004, c.2; AHRA), and the Canadian Institutes of Health Research (CIHR) *Updated Guidelines for Human Pluripotent Stem Cell Research.*
- Basic recombinant DNA technologies, such as gene deletion/duplication/modification
  - » Example: site-direct mutagenesis
  - » Example: current gene-replacement therapies, such as vector-delivery of insulin

Considerations and Questions

- Does the Royal Society definition appropriately cover Synthetic Biology?
- Does the proposed scope appropriately cover the issues that the Steering Committee would like to focus on?
- Is the Steering Committee comfortable with a growing list of examples to help clarify the scope as the work progresses?
  - » Pro: allows for an adaptive process that can evolve with evolving science and technologies to cover things not currently conceivable.
  - » Con: will require a very close attention to the amount of work that can reasonably be undertaken by the group and frequent checking in with the Steering Committee when new examples arise.
- What are the implications for the current language in the Terms of Reference and other materials? For example:
  - » "Steering Committee for the Oversight of Emerging Technologies (SCOET)"?

Appendix E

Synthetic Biology Steering Committee and Working Group			
Organization	**Activities**	**Time necessary / Schedule**	**Resources required**
Agriculture and Agri-food Canada, Strategic Policy Branch			
Canadian Food Inspection Agency, Animal Health Science Directorate			
Canadian Food Inspection Agency, Plant Health Science Directorate	Meetings, Prep, Options paper research/drafting	We are willing to commit the time necessary to fullfil the activities listed previously however, exact times and resources required is difficult to estimate at this point. We will evaluate time available to commit at regular intervals/milestones as the project progresses.	
Canadian Institutes of Health Research			
Defence Research and Development Canada			
Department of Fisheries and Oceans Canada (DFO)			
Department of Foreign Affairs, Trade and Development (DFATD)			
Departmetn of National Defence (DND)			
Environment Canada			
Health Canada, Safe Environments Directorate			
Health Canada, Science Policy Directorate			
Health Canada, Biologics and Genetic Therapies Directorate			
Industry Canada			
National Research Council			
NSERC (Corporate Planning and Policy Division)			
NSERC (Research Grants and Scholarships Directorate)			
Public Health Agency of Canada, Centre for Biosecurity	Research; coordination of work of participating partners; SC and WG secretariat; preparation of final drafts of documents		1.5 FTE
Public Safety Canada			

Edward Harrison

From: Cindy Pearson
Posted At: 2014-05-14 4:07 PM
Posted To: Microsoft Outlook Embedded Message

Subject: Re: For Comment: Oversight of Emerging Life Sciences Technologies (Formally Synthetic Biology)- Briefing Note and Appendices

Hi Nicole,
Thank you for coordinating the CFIA input into this initiative. Sorry that I am so slow to respond.
I'd like to provide some thoughts and questions for your consideration. Please forgive a few novice questions and comments, as I am new to this project. Also, I wonder whether I am perhaps presuming the outcomes of the project?

1. What are the timelines for this project?

2. Over the longer term, do you envision this project leading to the need for new programs being established?

3. Many thanks to Science Branch for representing the CFIA in this working group. As this moves more towards recommendations regarding how the government of Canada should address this evolving science, it would be helpful to also include programs branch representatives. I leave it to you to determine whether this would be informal PPB input through a Science Branch lead, or whether it would make sense to invite a PPB representative to the table as well. For example, I imagine that this is the type of project in which other groups would also be interested in? Could this have the potential to impact Fertilizer and Vet Biologics? Perhaps Feed as well? But please let me know if I am off base here, and that most of the responsibility for regulation of these products would actually be heading over to EC?

One way to manage this would be to add an extra consultation step when the "key recommendations" and "GoC framework" referenced in the next steps of the briefing note are developed (i.e.: consult internally across GoC before the recommendations are presented to management).

4. Has there been any early discussion as to whether an MC would be considered for obtaining funds to implement a new program? (OK, I am probably putting the cart waaaay before the horse with this question!)

5. The Terms of Reference, page 2 Guiding Principles, third bullet regarding responsibilities for follow-up actions indicates that we will follow up as per our mandates. I suppose that is OK, but I am worried to commit to following up on the framework without knowing what we would be getting into. Perhaps this wording could be further nuanced? Maybe something along the lines of: "responsibility to carry out follow-up actions identified in the GoC framework will be shared, within the respective mandates of departments and agencies according to internal resources and policies". Or something along those lines.

Thank you for the opportunity to comment,
Cindy

>>> Nicole van der Lee 2014-05-14 11:14 AM >>>
Hello Everyone,

I just wanted to take a moment and send out a second friendly reminder for comments. Comments are due back to the working group chair this Friday and I would greatly appreciate your input.

Thank you
Nicole

>>> Nicole van der Lee 2014-05-12 9:05 AM >>>
Hello Everyone,

This is just a quick reminder that comments were due last Friday. I would greatly appreciate it if you could provide me with any comments you may have so that they can be compiled and submitted.

Thanks you,
Nicole

>>> Nicole van der Lee 2014-05-01 7:22 PM >>>
Hello Everyone,

The email below was sent out by the Chair of the Working Group for the Oversight of Emerging Life Science Technologies (formerly Synthetic Biology Working Group). The email requests that comments are provided on behalf of each working group members department/agency on the attached documents. As such, PBRA is happy to offer to compile and roll-up comments on behalf of the CFIA. It is also important to note that in addition to comments they are requesting that resources be identified (including human resource and/or financial cost) to assist with the completion of a revised options paper.

At this time we are sending the documents out for comment to the steering committee and working group representatives from the CFIA, as well as Plant Health Research and Strategies and the Plant Biosafety Office. If we have missed any groups/individuals that you think should be involved, please contact me and I will ensure to forward this message along to them.

In terms of time lines, they are looking for comments by mid-May, thus I would appreciate it if I could receive **comments back by May 9th**. For convenience, I have saved all the documents in RDIMS so that comments can be input directly into the files.

Should you have any questions please feel free to contact me.

Thank you,
Nicole

Nicole van der Lee, M.Biotech.
Risk Assessor - Biotechnology | Ã‰valuatrice des risques - biotechnologie
Plant and Biotechnology Risk Assessment Unit | UnitÃ© d'Ã©valuation des risques des vÃ©gÃ©taux et des produits de la biotechnologie
Canadian Food Inspection Agency | Agence canadienne d'inspection des aliments
1400 Merivale Road | 1400 chemin Merivale,
Ottawa, ON K1A 0Y9
nicole.vanderlee@inspection.gc.ca
Telephone | TÃ©lÃ©phone 613-773-6552
Government of Canada | Gouvernement du Canada

>>> Dusan Valachovic <dusan.valachovic@phac-aspc.gc.ca> 2014-04-29 10:11 AM >>>
Dear Working Group members;

As you will have seen from the minutes from the last Steering Committee

meeting, we have been asked to prepare a joint briefing note that will be routed to respective Deputy Ministers. The BN will provide an overview of our activities to date and seek approval of the plan, including resources needed for its completion.

Attached are draft memo and appendices - please send us your comments by May 16th so we can update the draft. We will then leave it up to each of you to refine and start the process to route the BN to your respective Deputy Ministers.

As noted, the Steering Committee asked that the BN include an estimate of the resources that will be required to draft the options paper. Could you please take a look at the Appendix E (Outline deck) and identify areas of the paper where your department/agency will be able to contribute and estimate the human resources costs (or financial if you think there will be expenses to incur). PHAC can lead the group work on the majority of the paper; however, we propose that Jamie Flammenbaum be the lead on the ethical considerations and Andrew Halliday be the lead on the international context. If your department or agency should be the lead on any of the remaining content, please put your name forward.

Updating the assessment is the real research component and will likely be the most resource intensive. PHAC can lead this work, but it will be important to have other working group members participate in this research, so please put your name forward if you can contribute.

Thank you.

Dusan Valachovic
Policy Analyst
Centre for Biosecurity / Centre de la BiosÃ»retÃ©
Public Health Agency of Canada / Agence de la santÃ© publique du Canada
100 Colonnade Road, room 1007-48 / 100 chemin Colonnade, piÃ¨ce 1007-48
Ottawa

Cindy Pearson - Fwd: AHTEG_travel__Bonn.docx

From: Cindy Pearson
To: Olivier Morin
Date: 2014-07-04 4:23 PM
Subject: Fwd: AHTEG_travel__Bonn.docx
Attachments: AHTEG_travel__Bonn.docx

interesting. I think that this will be something that needs to be discussed prior to the next COP/MOP meeting in the fall. I think that Luis will again lead the prep work for the COP/MOP, but will engage us as well.
C

Cindy Pearson - AHTEG_travel__Bonn.docx

From: Philip Macdonald
To: Tracey Knowles
Date: 2014-07-04 4:17 PM
Subject: AHTEG_travel__Bonn.docx
CC: Cindy Pearson; Jim.Louter@ec.gc.ca; Kirsten Finstad; Luis Barnola
Attachments: CFIA_ACIA-#5642232-v1-AHTEG_travel__Bonn.docx

My trip report for the AHTEG meeting in Bonn.

Phil

s.15(1)
s.21(1)(a)
s.21(1)(b)

SCIENCE BRANCH TRAVEL REPORT

NAME OF PARTICIPANT(S): Philip Macdonald

DATE OF TRAVEL: June2-6, 2014, Bonn Germany

PURPOSE OF TRAVEL: To participate in the face to face meeting of the Ad Hoc Technical Experts Group (AHTEG) on Risk Assessment and Risk Management of Living Modified Organisms

LOCATION (CITY/COUNTRY): Bonn, Germany

SUMMARY OF ACTIVITIES: The AHTEG was established at the 4th Meeting of the Parties to the Cartegena Protocol on Biosafety. The key charge was to develop further guidance on Annex 3 of the Protocol. Following that charge, the AHTEG has developed specific guidance in the form of a Roadmap which is to apply to the risk assessment of all types of living modified organisms (LMO), and specific guidance on LMOs with stacked traits, LMOs with stress tolerance traits, LMO mosquitoes, LMO trees and Monitoring. The documents have been refined during the periods between the face to face meetings and there has been a scientific review. At the last Meeting of the Parties, the AHTEG was restructured with some new members and charged with ensuring that the guidance was tested and comments considered. The face to face meeting was to discuss the outcomes of the testing of the guidance, discuss how the outcomes of the testing could be used, develop a process for prioritizing topics for further guidance, discuss the alignment and consistency of the training materials that have been prepared to accompany the guidance and to discuss the process for adding new references to the guidance.

ANALYSIS OF INFORMATION GATHERED/POTENTIAL IMPACT ON PROGRAM DESIGN WITHIN CFIA:

-

- The current draft of the Roadmap, although vastly improved, is still filled with speculative risks and prescriptive language. The document is not yet consistent with some of the best practices described by international organizations such as the OECD or the regulatory approaches of more experienced countries like Australia or the United States.

-

- There are over 89 pages of comments that have been derived from the testing of the guidance and some parties provided extensive suggestions for improvements that

s.15(1)
s.19(1)
s.21(1)(a)
s.21(1)(b)

included simplifying the language, improving the alignment of the guidance with the Protocol and extensive rewrites to some sections

- and the Secretariat chose to concentrate on the rating exercise for the guidance, which was primarily positive and minimize the comments from the testing. Canada, were singled out by some AHTEG members as outliers because their ratings of the usefulness of the guidance were quite low. Some parties argued that the ratings had little meaning because the questions were poorly designed.
- A group of 4 AHTEG members from Parties was chosen to review the comments from the guidance, rank them as: Statements that require no changes; comments that have specific text suggestions, comments that would require changes but have no specific text changes and suggested editorial changes.
- Canada, objected that the group would group the comments and make what they believed were the necessary changes but the AHTEG would only get to comment on the outcomes after the process was complete. The same group also objected that this work was going to be characterized as updating rather than incorporating suggested changes arising from the testing of the guidance.
- A report was prepared from the meeting that indicated that the guidance was endorsed by the AHTEG as is with a forward process to update the guidance and endorsed a process for the development of further guidance
- Canada, objected that this was not the view of the AHTEG and asked to have the text changed to "Parties recommend". refused and refused to have either a description of the process followed or the objections that had been stated incorporated into the report. decision was supported by the Parties at the AHTEG.
- Canada requested that capture the discussion over the use of the term "update" rather than "incorporate comments" but this was not supported by the Parties
-

APPROX. COST OF TRAVEL: $2500

DATE SUBMITTED: July 4, 2014

Approved by Cameron Duff

Cindy Pearson - Re: Researcher looking for regulatory guidance re: cisgenics

From: Cindy Pearson
To: Annie Savoie; Luc Bourbonniere; Philip Macdonald
Date: 2014-07-15 4:07 PM
Subject: Re: Researcher looking for regulatory guidance re: cisgenics
CC: PBO group
Attachments: Genome Canada funding: Cisgenic wheat and barley cultivar registration - Policy change of CFIA on GMO to include Cisgenics; wheat and potato cultivar development through cisgenics with gene replacement technology; 2014-Sander-CRSPR-CAS-Nature_1.pdf

Hi everyone,
Here is the scoop - the researcher contacted me on Friday and with a holiday day yesterday I haven't yet had a chance to respond.

This researcher has now contacted us twice:
1. Back in April with questions on cisgenics: I had replied with our standard links to the website to learn about our reg programs and to suggest a pre-sub. I thought that I had forwarded this to you guys? Sorry if I didn't do so. The second and third attachments are from April to bring you up to speed on his research and my original response.

2. On Friday, we were contacted again with requests regarding CFIA (and HC) policies and for the CFIA to be a collaborator in their genome Canada project.

I propose the following response:

- Let him know that the CFIA could not be a collaborator in a research project of this nature.
- We would be happy to meet with him to explain the regulatory requirements.

I think that we (CFIA + HC) would need to meet in advance in order to discuss our current policy positions.

thanks,
Cindy

>>> Annie Savoie 2014-07-15 2:29 PM >>>
Can we not just send the guidelines.....? not sure what more to add.

We are available before that time if need be. After that date would be difficult,

Annie

>>> On 2014-07-15 at 2:03 PM, in message <53C53A7E.CEA4.005C.0@inspection.gc.ca>, Philip Macdonald wrote:

> Hey Guys,

I was contacted this morning by | from Genome Quebec about a research scientist at MacDonald College who is developing a cis-genic barley and is seeking some help with the regulatory side, mostly an understanding of the requirements. He is in competition for a $15 million research grant and needs to have some answers for the review panel. Would you or a delegate be available to discuss the regulatory pathway before July 27? thinks has already talked to you Cindy.

let me know.

Phil

Cindy Pearson - Re: Cisgenic with genome editing to transfer resistance to late blight genes to potato

From: Cindy Pearson <Cindy.Pearson@inspection.gc.ca>
To:
Date: 2013-12-04 11:57 AM
Subject: Re: Cisgenic with genome editing to transfer resistance to late blight genes to potato
CC: Elizabeth Prentice-Hudson <Elizabeth.Prentice-Hudson@inspection.gc.ca>, ...

Hello
Thank you for contacting us with questions regarding the regulatory system in Canada.

The Canadian Food Inspection Agency and Health Canada work together to assess the safety of plants with novel traits. Plants with novel traits can include plants produced through biotechnology, genetic engineering or conventional breeding techniques. These plants cannot enter the marketplace unless authorized by the CFIA and HC's for use as food, feed and release into the environment.

I'd like to start by providing a link to our website that explain our program for the regulation of Plants with Novel Traits: http://www.inspection.gc.ca/plants/plants-with-novel-traits/eng/1300137887237/1300137939635

I recommend that you take a moment to review Directive 2009-09 on our website. This directive aims to assist breeders, developers and importers of new plant lines in determining if their plant is regulated under Part V of the *Seeds Regulations* prior to its environmental release: http://www.inspection.gc.ca/plants/plants-with-novel-traits/applicants/directive-2009-09/eng/1304466419931/1304466812439
If you are producing a plant with a novel trait, there may be additional regulatory requirements associated with use as livestock feed and use a food. If helpful, I would be happy to pass along your email to the responsible groups to engage them as well?

I'd be happy to discuss anytime. I can be reached at the contact information below.
Best regards,
Cindy

Cindy Pearson
cindy.pearson@inspection.gc.ca
(613) 773-7149
Facsimile / Télécopieur : (613) 773-7144
A/National Manager, Plant Biosafety Office
Canadian Food Inspection Agency
I/Gestionnaire nationale, Bureau de la biosécurité végétale
Agence canadienne d'inspection des aliments
59 Camelot Ct
Ottawa ON K1A 0Y9
Government of Canada | Gouvernement du Canada
www.inspection.gc.ca

>>> Elizabeth Prentice-Hudson 2013-12-04 9:11 AM >>>
Hello all;

Essential derivation is not yet in place in Canada - a principle of the 1991 UPOV Convention. At the same time, a new variety that may be essentially derived from the initial variety does not limit the use of the original variety for further breeding work. Potential limitations come when the breeder wants to commercialize the new, essentially derived variety. At that point, the breeder of the original variety may have claim to the new, essentially derived variety.

Elizabeth

>>> Mark Forhan 2013/12/04 1:00 AM >>>
Sima,

Can you please verify comment regarding **Russet Burbank** variety of Potato and pull the original file to verify if you find there is no Canadian Representative mentioned in the PRS database. Unlike Plant Breeders Rights, there is no situation for expiry of variety registration (only cancellation of variety by request of Canadian Representative or for cause by the Registrar). One thing I do know from my breeding days is that a modified Russet Burbank, as he proposes, would trigger the commonly understood "essentially derived" assessment by FIS standards (Federation International de Semmences). If the variety is public domain, then he should be free and clear.

If the 'new' variety was phenotypically identical to the existing variety then we could not register the variety - this may be a problem for him but one step at a time. We can work with him on this aspect (possibility of naming Russet Burbank XX, where XX is a suffix on the original name denoting a modified Russet Burbank).

The Plant Biosafety Office can address the rest of his inquiry regarding the trait in question and the method of generating it in this previously registered variety.
-Mark

Canadian Food Inspection Agency | Agence canadienne d'inspection des aliments

Mark Forhan
Tel/tél: (613) 773-7148 |
email/courriel:
mark.forhan@inspection.gc.ca
Facsimile / Télécopieur : (613) 773-7144
Senior Specialist, Variety Registration Office, Canadian Food Inspection Agency
Spécialiste principal, Section de l'enregistrement des variétés, Agence canadienne d'inspection des aliments
59 Camelot Drive, Ottawa, ON K1A 0Y9 | 59 Promenade Camelot, Ottawa ON K1A 0Y9
Government of Canada | Gouvernement du Canada
www.inspection.gc.ca
CFIA toll free phone |
Numéro sans frais: 1-800-442-2342

>>>

From: Elizabeth Prentice-Hudson

To:

CC: Cloutier, Renee; Forhan, Mark; Henri, Tamala; Pearson, Cindy

Date: 01:00 PM 2013-12-03

Subject: Re: Cisgenic with genome editing to transfer resistance to late blight genes to potato

Hello

You have contacted the Plant Breeders' Rights office, responsible for the administration of the Plant Breeders' Rights (PBR) Act which grants plant breeders' rights (PBR) to breeders of new varieties of plants. To be eligible for protection under PBR, a variety must be new, distinct, uniform and stable. As the potato variety, 'Russett Burbank', has been sold in Canada for several years, it does not qualify for protection under the PBR Act, and is therefore considered a public variety. If, in the future, you develop a new variety that would meet the criteria for protection under the PBR Act, you could make application to our office for protection. The fees for protecting a new variety include: application ($250), examination ($750) and grant of rights ($500) for a total of $1500. (For further information on how to apply for a plant breeder's right, please visit our website at http://www.inspection.gc.ca/plants/plant-breeders-rights.) Feel free to contact the office if you have any additional questions.

In the event that you have not yet contacted either the Plant Biosafety Office or the Variety Registration Office, I have copied, Cindy Pearson, Acting National manager for the Plant Biosafety Office (responsible for administering applications for Plants with Novel Traits) and Mark Forhan, Senior Specialist, Variety Registration Office, on this message. They may be able to provide you with additional information.

Kind regards,

Elizabeth

Elizabeth Prentice-Hudson
Examiner, Plant Breeders' Rights (PBR)/ Examinatrice, Bureau des obtentions végétales
Canadian Food Inspection Agency / Agence canadienne d'inspection des aliments
2nd floor - 59 Camelot Drive/ 2ième étage - 59, rue Camelot
Ottawa, Ontario/ Ottawa (Ontario)
K1A 0Y9
(613) 773-7139
Fax: (613) 773-7261>> 2013/11/28 3:39 PM >>>

Dear Tamala

I see with AAFC cultivar registration the cultivar 'Russet Burbank' – no representative. Please let me know if I can use this cultivar to transfer a set of genes we have identified in potato against late blight and register on my or McGill name – would this be a 'Russet Burbank with novel traits'? There are now new protocols and I think we can meet your requirements to transfer the genes without any foreign DNA.
To sign an agreement with a funding agency please let me know a contact person in CFIA for further collaboration all the way to cultivar registration. How much would be your fee.
Sincerely,

Plant Science Department
McGill University, 21 111 Lakeshore Road
Ste-Anne-de-Bellevue, QC, Canada H9X3V9
Tel:
http://www.mcgill.ca/plant/faculty/
http://www.mcgill.ca/globalfoodsecurity/research-initiatives/

Cindy Pearson - Genome Canada funding: Cisgenic wheat and barley cultivar registration - Policy change of CFIA on GMO to include Cisgenics

From:
To: Cindy Pearson <Cindy.Pearson@inspection.gc.ca>
Date: 2014-07-11 11:33 AM
Subject: Genome Canada funding: Cisgenic wheat and barley cultivar registration - Policy change of CFIA on GMO to include Cisgenics
Attachments: Re: Cisgenic with genome editing to transfer resistance to late blight genes to potato

Dear Cindy
I am, as a PI, applying for Genome Canada funding on 'Development of fusarium head blight and mycotoxin resistant barley and wheat cultivars through functional genomics'. I have excellent support from the Genome Quebec team. Yesterday we had a meeting with them here in our campus and I asked them if I could involve a CFIA person as a collaborator in my application. They fully support this. So please let me know if you could officially collaborate with us in this project. Or suggest a name if you think someone else is responsible.

1. What I need: Policy change of CFIA to include revised guidelines to approve Cisgenic cultivars, which are not GMO, safe for human and animal consumption.
2. Why this policy change: I understand all technologies used for cisgenics are not safe. Here is what we use and based on Technology Concept proved in Arabidopsis can you approve the cisgenic wheat and barley as not a GMO and are cisgenic cultivars produced based on proved safe technology. If CFIA is involved in the project then they can visualize how the cisgenic cultivar is generated and based on the concept of sound technology all other requirements to test the safety of GMO can be avoided.
3. We intend to identify candidate genes for resistance in wheat and barley to fusarium head blight fungus. These wheat and barley genes will be cloned. Protoplasts of elite cultivars of wheat and barley are produced and through electroporation, the construct of resistance genes in CRISPR-Cas9 system will be introduced into elite protoplast and regenerated into a plant. Thus, if it works, this technology doesnot use any agroinfiltration, etc., it would have no foreign DNA or vector backbone DNA. Cisgenic means transfer of genes between sexually compatible plants. So gene comes from within species – different genotypes. So no foreign DNA or Gene. The CRISPR-Cas9 has been shown in Arabidopsis, through complete genome sequencing, the intended gene is introduced in the exact intended genomic location, no other mutations, etc. Also the somatically introduced genes are integrated into the germ cells. So there is no reason why other safety tests are needed. Your collaboration is highly appreciated.

Best

Plant Science Department
McGill University, 21 111 Lakeshore Road
Ste-Anne-de-Bellevue, QC, Canada H9X3V9
Tel: |
http://www.mcgill.ca/plant/faculty/
http://www.mcgill.ca/globalfoodsecurity/research-initiatives/

Cindy Pearson - wheat and potato cultivar development through cisgenics with gene replacement technology

From:
To: "Pearson, Cindy (Cindy.Pearson@inspection.gc.ca)" <Cindy.Pearson@inspect...
Date: 2014-04-03 11:05 AM
Subject: wheat and potato cultivar development through cisgenics with gene replacement technology
CC:
Attachments: 2014-Sander-CRSPR-CAS-Nature.pdf

Dear Cindy
Currently, I have a project funded by the IDRC-DFATD (2012-2014), among others, to identify late blight resistance genes based on OMICs (genomics, proteomics and metabolomics) approach. Both in Canada and in Colombia growers apply 10-15 applications of fungicides, per crop, to manage this disease. Now we have identified a set of few genes both in Canadian and Colombian potato cultivars with very high levels of resistance to late blight. Because of sexual incompatibility it is very difficult to transfer genes between potato genotypes. IDRC-DFATD considers ours to be one of the best projects and supporting a second phase. I am submitting this project, for 5 million dollars for 42 months, by April 12, 2014. In this initiative I have proposed to produce cisgenic Russet Burbank, and also two other Colombian elite cultivars in collaboration with Colombian scientists, one of the most commonly cultivated potato in North America but still susceptible to later blight. I understand this is generally considered as a (cisgenic) cultivar with novel traits. We propose to transfer late blight resistance genes from resistant potato cultivars, may be also iron and zinc accumulating genes in future, to the elite cultivars of Canada and Colombia. We intend to construct late blight resistant genes, from a resistant cultivar, using CRISPR-Cas system, and then introduce this gene construct to the protoplast of elite cultivar cells – by microinjection technology available at McGill. Since the CRISPR-Cas is a restriction enzyme, it will replace the susceptible gene with the resistant ones in the same genomic location, based on published information attached, and thus, we expect not to leave any foreign DNA in the elite cultivar. Since no foreign gene has been introduced in this case we expect no modification at all to the elite cultivars, and thus, hope to get your full support in developing and registering cisgenic Russet Burbank in Canada. We intend to distribute this cultivar to all poor countries as Canadian Food Security contribution – free of cost.
We would like to work in collaboration with you in this project. I recently obtained a grant from Ministry of Quebec (MAPAQ) to develop a cisgenic elite cultivar for resistance to fusarium head blight of wheat, another devastating disease of North America. We have already identified some candidate genes. We would like to involve a team of researchers to develop these cultivars. I appreciate your collaboration and guidance.
Thanking you,
Sincerely,

Plant Science Department
McGill University, 21 111 Lakeshore Road
Ste-Anne-de-Bellevue, QC, Canada H9X3V9
Tel:
http://www.mcgill.ca/plant/faculty/
http://www.mcgill.ca/globalfoodsecurity/research-initiatives/

Martine de Graaff - Fwd: RE: Genome Canada funding: Cisgenic wheat and barley cultivar registration - Policy change of CFIA on GMO to include Cisgenics

From: Martine de Graaff
To: Bourbonniere, Luc; Macdonald, Philip; Savoie, Annie
Date: 2014-07-28 11:17 AM
Subject: Fwd: RE: Genome Canada funding: Cisgenic wheat and barley cultivar registration - Policy change of CFIA on GMO to include Cisgenics

I agree with acting independently, but I think that misses his intention, as he hopes to avoid all regulation:)

I'll cc you all on my response. Not sure if I can arrange a call this week as I'll be in and out (and off) most of the week. I have to leave for an hour now, but I can see if I can work something in this week...

>>> On 2014-07-28 at 11:15 AM, in message <53D668FC.EE1 : 92 : 52900>, Annie Savoie wrote:

> Also note that we are not part of any team when it comes to a regulated party situation. We need to act independently and at arms length. I can take the call with you this week before end of day wed if you want?
>
> A
>
> >>> On 2014-07-28 at 10:34 AM, in message <53D65F7B.C5B : 200 : 11368>, Martine de Graaff wrote:
>
> > Hi all,
> >
> > As you can read below, is still hoping for additional help from us on his research team, and b/c we won't be able to schedule the meeting for another several weeks, I was thinking it might be important to address his expectation that we will be joining his team.
> >
> > As such, I'm proposing that I contact him with a general statement on novelty (without going into detail as I would rather each individual group address their triggers, etc on a call with him) and that unfortunately we will not be able to commit to his research team due to current resources and the fact that any future policy work would require a lot of time, resources and consultation that we have not planned for...or something more eloquent if you have any comments off the tops of your heads.
> >
> > thanks,
> > Martine
> >
> > >>> On 2014-07-25 at 8:38 AM, in message
> > <06CB2305D543A948AACE28B18737FBDA3B303731@EXMBX2010-7.campus.MCGILL.CA>, '
> > wrote:
> >
> > > Hi Martine
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Tel:
http://www.mcgill.ca/plant/faculty/
http://www.mcgill.ca/globalfoodsecurity/research-initiatives/

From:
Sent: Thursday, July 24, 2014 4:07 PM
To: Martine de Graaff;
Subject: RE: Genome Canada funding: Cisgenic wheat and barley cultivar registration - Policy change of CFIA on GMO to include Cisgenics

Martine,

I will let answer the question. However, please note that I am not available the week of August 18.

De : Martine de Graaff [mailto:Martine.DeGraaff@inspection.gc.ca]
Envoyé : 24 juillet 2014 15:51
À :
Cc :
Objet : RE: Genome Canada funding: Cisgenic wheat and barley cultivar registration - Policy change of CFIA on GMO to include Cisgenics

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Canadian Food Inspection Agency
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Telephone: (613) 773-7147
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s.19(1)

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2014-07-11 11:32 AM

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Martine de Graaff - RE: Genome Canada funding: Cisgenic wheat and barley cultivar registration - Policy change of CFIA on GMO to include Cisgenics

From: Martine de Graaff
To:
Date: 2014-07-30 5:21 PM
Subject: RE: Genome Canada funding: Cisgenic wheat and barley cultivar registration - Policy change of CFIA on GMO to include Cisgenics
CC: Davis, Sarah G.; Macdonald, Philip; Savoie, Annie; Steele, Marina; g...

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From: Cindy Pearson
To: Annie Savoie; Luc Bourbonniere; Martine de Graaff; Philip Macdonald
Date: 2014-07-15 5:14 PM
Subject: Fwd: Re: Genome Canada funding: Cisgenic wheat and barley cultivar registration - Policy change of CFIA on GMO to include Cisgenics
Attachments: Re: Genome Canada funding: Cisgenic wheat and barley cultivar registration - Policy change of CFIA on GMO to include Cisgenics

Hi,
Here's what I wrote to the researcher.
C

Martine de Graaff - Re: Genome Canada funding: Cisgenic wheat and barley cultivar registration - Policy change of CFIA on GMO to include Cisgenics

From: Cindy Pearson
To:
Date: 2014-07-15 5:13 PM
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Edward Harrison - Fwd: RE: Genome Canada funding: Cisgenic wheat and barley cultivar registration - Policy change of CFIA on GMO to include Cisgenics

From: Edward Harrison
To: Martine de Graaff
Date: 2014-08-06 12:52 PM
Subject: Fwd: RE: Genome Canada funding: Cisgenic wheat and barley cultivar registration - Policy change of CFIA on GMO to include Cisgenics

Hey Martine

My first thought - (I haven't read the source info paper) - what literature do we have on the rationale for the cisgenic potato trials? Can you dig up any briefing notes, docs, rationales, summary of policy decisions (talk to Natalia?) He's basically describing a very clean (molecular-wise) cisgenic transformation. And since we have already made a decision on this (potato?) you could refer to that during your meeting?

I'll read the background document as well and get back to you

>>> Martine de Graaff 2014-08-06 11:52 AM >>>

>>> On 2014-08-06 at 11:48 AM, in message
<06CB2305D543A948AACE28B18737FBDA3B306A7F@EXMBX2010-7.campus.MCGILL.CA>,
wrote:

> Dear Martine
> I understand that your participation as a co-applicant may be inappropriate. I agree. However, your collaboration to guide us in the right direction is very important to avoid unnecessary costly but still not very practical outcomes. I understand that not all Cisgenic crops are safe. The genetic engineering technology used play a significant role. The CRISPR-Cas system beats them all.
>
> What we have in Cisgenics based on CRISPR-Cas9 technology to replace genes; following are the proof of concepts. These are clearly different from the GMOs or even other gene transfer technologies:
>
> 1. No trans or foreign gene is introduced
> 2. No vector DNA is left behind
> 3. No random mutation as proved in Arabidopsis – genome resequencing, which is almost impossible in complex genomes
> 4. No introduction of genes to a random location in the genome; rather it replaces SNPs in a specific genomic location. This SNP can be detected in our cisgenic cultivars any time.
> 5. The gene/SNP replacement is an inheritable character as proved in Arabidopsis.
> 6. Cisgenic is better than the conventional breeding as the latter leads to transfer of undesirable genes due to linkage drag. The time is reduced from ten years to 3-4 years. No monopoly, when standardized any molecular biologist can replace the genes in their own favorite cultivars, thus increasing the genetic diversity of that genotype. Finally the science can deliver what farmers need.
>
> Thus, these genomic information can prove better than the food analysis that there are no variations in the food quality. But there is difference in the amount of same food contents or metabolites that also give resistance in plants to pathogen attack.

We need authorization to cultivate these cisgenics under field conditions to assess economic yield losses, as required by Genome Canada. It may be possible to release some cisgenic cultivars for commercial use in the fourth year. How do we go about this. May be you guys have to come up with a list of safe technologies, if any satisfy all, then the cultivar can be released for commercial use. I think the above technology can meet all your concerns.
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From: Martine de Graaff [mailto:Martine.DeGraaff@inspection.gc.ca]
Sent: Wednesday, July 30, 2014 5:21 PM
To:
Cc: gaetano.cianciarelli@hc-sc.gc.ca; luc.bourbonniere@hc-sc.gc.ca; Annie Savoie; Marina Steele; Philip Macdonald; Sarah G. Davis
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AAFC

From: Barnola, Luis
To: Michelazzi. Karl, Dollard. Cheryl, Jim.Louter@ec.gc.ca, Judith.Gelbman@i...
CC: Doan. Darcie, Angela.Bilkhu@international.gc.ca, Macdonald. Philip, Fins...
Date: 2014-11-03 3:42 PM
Subject: RE: Cartagena Protocol: results (summary) of the MOP-7 and request for nominations of experts to the
Attachments: AAFCAAC-#100982413-v2-CARTAGENA_PROTOCOL_-_MOP-7_-_SUMMARY_REPORT_BY_CANDEL_-_OCT_02_2014.DOCX

Dear Colleagues,

My apologies. Last Friday I sent you the wrong summary table. Attached you'll find the correct one including the list of objectives and outcomes from the last Cartagena meeting (MOP-7).

Best regards,
Luis Barnola

From: Barnola, Luis
Sent: October-31-14 5:33 PM
To: Michelazzi, Karl; Dollard, Cheryl; 'Jim Louter'; 'Judith Gelbman'; de Graaff, Martine; Morin, Olivier; 'Rachel Geddy'; 'Tannis Beardmore'; Anderson, Laura; 'Caroline Mimeault'; Colville, Adam; 'Debby Barsi'; Doan, Barbara; Doucette, Nicholas; Foster, Liz; Goodwin, Jarett; 'Janet Beardall'; 'Jennifer Fellows'; 'Jessica Thomson'; Pearson, Cindy; 'Phyllis Dale'; Tolusso, Giuliano; Van Neste, Erika; 'Robert.Brookfield@international.gc.ca'; 'Beth.Newcombe@international.gc.ca'; 'Sherry Walker'; 'Laura Anderson'; Dormann, Nataliya; 'Ryan Tolusso'
Cc: Doan, Darcie; 'Angela Bilkhu'; Macdonald, Philip; Finstad, Kirsten; 'John Moffet'
Subject: Cartagena Protocol: results (summary) of the MOP-7 and request for nominations of experts to the online forum on risk assessment--YOUR RESPONSE NEEDED BY COB NEXT FRIDAY NOVEMBER 14, 2014

Dear Colleagues,

The 7th meeting of the Conference of the Parties serving as the meeting of the Parties to the Cartagena Protocol on Biosafety (MOP-7) took place in Pyeongchang, Republic of Korea, from September 29 to October 3 2014. As observers, the Candel maintained a low profile at the meeting and worked in the corridors with like-minded Parties to build support for Canadian positions. The tone of the discussion and the positive outcomes of this meeting, as summarized in the table attached, showed a more balanced approach to addressing the environmental safety and trade of LMOs.

In addition, please note that nomination of experts for the online forum on risk assessment is currently open so we would like to invite you, or your colleagues with expertise on environmental risk assessment of LMOs, to confirm your interest in participating in the Open-ended Online Expert Forum on Risk Assessment and Risk Management no later than Friday, November 14, 2014. Currently, the list of participants to the Online Expert Forum includes 6 Canadian experts representing DFO, CFIA and EC. However, I believe that only CFIA/Phil Macdonald is active in this file. As a matter of fact, Phil attended the MOP-7 and was reconfirmed as a member of the AHTEG on risk assessment and risk management.

If you have any questions regarding the MOP-7, the nomination of experts or in general about the Cartagena Protocol, please contact me at your earliest convenience.

Best regards,
Luis Barnola
613-773-2489

<< File: AAFCAAC-#4548051-v2-MISB_-_TAND_-_TTPD_-_TO_DO_LIST_-__TTPD-BIOTECH_-_2013-2014.DOCX >>

From: secretariat [mailto:SECRETARIAT@cbd.int]
Sent: October 28, 2014 4:51 PM
To: List of BCH NFP; List of Biosafety NFP
Subject: CBD Notification 2014-125 - Nomination of experts to the Open-ended Online Expert Forum on Risk Assessment and Risk Management under the Cartagena Protocol on Biosafety

Date: 27 October 2014
From: Executive Secretary, Convention on Biological Diversity
To: Cartagena Protocol National Focal Points, Biosafety Clearing-House National Focal Points, CBD National Focal Points (where CPB focal points have not yet been designated), Relevant Organizations
Subject: Nomination of experts to the Open-ended Online Expert Forum on Risk Assessment and Risk Management under the Cartagena Protocol on Biosafety
Thematic area: Cartagena Protocol on Biosafety
Ref.: SCBD/BS/MPM/DA/83988

NOTIFICATION
No. 2014-125

Madam/Sir,

In its decision BS-VII/12, paragraph 4, the Conference of the Parties serving as the meeting of the Parties to the Cartagena Protocol on Biosafety (COP-MOP) decided to extend the Open-ended Online Expert Forum (Online Forum) on Risk Assessment and Risk Management and the Ad Hoc Technical Expert Group (AHTEG) on Risk Assessment and Risk Management with the revised terms of reference annexed hereto, and to expand the composition of the AHTEG by adding one new member from each region.

In paragraph 8 of decision BS-VII/12, the COP-MOP invited Parties, other Governments and relevant organizations to confirm the nominations of their experts who are currently participating in the Online Forum, and requested the Executive Secretary to remove the records of experts whose nominations are not confirmed.

The COP-MOP further invited Parties, other Governments and relevant organizations to nominate additional experts to join the Online Forum using the format for the nomination of experts to the Roster of Experts.

Accordingly, I am pleased to invite you (i) to confirm the nominations of experts from your country or organization, as appropriate, who are currently participating in the Open-ended Online Expert Forum on Risk Assessment and Risk Management, and (ii) to nominate additional experts from your country or organization, as appropriate, who are actively involved in risk assessment and risk management, to participate in the Open-ended Online Expert Forum on Risk Assessment and Risk Management.

Confirmation of nominations of experts currently participating in the Online Forum

Confirmation of experts who are currently participating in the Online Forum may be done by National Focal Points or Heads of organizations, as appropriate, via correspondence to secretariat@cbd.int confirming the name of the expert for continued participation in the Open-ended Online Expert Forum on Risk Assessment and Risk Management. The list of participants to the Online Forum is available at http://bch.cbd.int/onlineconferences/participants_ra.shtml.

The confirmation of experts is to be done as soon as possible but no later than 30 November 2014. The records of experts who are not confirmed will be removed from the Online Forum as requested by the

s.19(1)

COP-MOP.

Nominations of new experts to the Online Forum

Nominations for new experts to the Online Forum are to be submitted electronically at https://bch.cbd.int/onlineconferencing/riskAssessment/expertNomination.shtml by Parties and other Governments (access restricted to National Focal Points) or at https://bch.cbd.int/onlineconferences/nominationOrgs_ra.shtml by relevant organizations.

Only in the event of difficulty submitting this information online, a common format for the nomination of a biosafety expert may be downloaded, completed and sent to the Secretariat at secretariat@cbd.int. (The offline format for nominating experts is available at https://bch.cbd.int/resources/common%20formats/nationalrecord_07_biosafetyexperts_en.doc?download. Nominations that are not submitted electronically through the Biosafety Clearing-House must (a) be completed and signed by the Cartagena Protocol National Focal Point (for nominations by Parties and other Governments) or Head of organization (for organizations), (b) contain clear reference to the Open-ended Online Expert Forum on Risk Assessment and Risk Management and (c) be sent to the Secretariat via email (secretariat@cbd.int), fax (+1-514-288-6588) or postal mail (Secretariat of the Convention on Biological Diversity, 413 rue Saint-Jacques, suite 800, Montreal, Quebec, H2Y 1N9, Canada).)

Nominations for new experts to the Online Forum will be accepted on an ongoing basis, however, to be considered as a candidate for the AHTEG on Risk Assessment and Risk Management, nominations for experts to the Online Forum are to be received before 30 November 2014.

Selection of new AHTEG members

To expand the composition of the AHTEG on Risk Assessment and Risk Management, one new member from each of the five geographical regions will be selected by the Secretariat, in consultation with the COP-MOP Bureau, from among those experts nominated to the Online Forum by Parties, taking into account their expertise and gender balance in accordance with the Consolidated modus operandi of the Subsidiary Body on Scientific, Technical and Technological Advice of the Convention on Biological Diversity. (Available at http://www.cbd.int/doc/publications/bs-rules-en.pdf.)

The selection of the five new AHTEG members will take place in early December 2014.

The text of this notification is also available on the CBD website at:
http://www.cbd.int/doc/notifications/2014/ntf-2014-125-bs-en.pdf

Please accept, Madam/Sir, the assurances of my highest consideration.

Secretariat of the Convention on Biological Diversity
United Nations Environment Programme
413 Saint-Jacques Street, Suite 800
Montreal, Quebec, Canada
H2Y 1N9

Tel: +
Fax: +1 514 288 6588
E-mail: secretariat@cbd.int
Web: http://www.cbd.int

Annex

TERMS OF REFERENCE FOR THE OPEN-ENDED ONLINE FORUM AND AD HOC TECHNICAL EXPERT GROUP ON RISK ASSESSMENT AND RISK MANAGEMENT

Methodology

1. Taking into account the results of the testing process, established in decision BS-VI/12, the Guidance on Risk Assessment of LMOs shall be revised and improved in accordance with the following mechanism:

(a) After the seventh meeting of the COP-MOP, the Secretariat will group the original comments provided through the testing of the Guidance. The grouping will be done in the form of a matrix based on the following categories: statements that do not trigger changes; editorial and translational changes; suggestions for changes without a specified location in the Guidance; and suggestions for changes to specific sections of the Guidance (sorted by line numbers);

(b) The AHTEG shall review the grouping of comments done by the Secretariat and work on the suggestions for changes;

(c) The AHTEG shall streamline the comments by identifying which suggestions may be taken on board and providing justification for those suggestions that may not be taken on board. The AHTEG will also provide concrete text proposals for the suggestions to be taken on board with a justification where the original suggestion was modified;

(d) The Open-ended Online Forum and the AHTEG shall subsequently review all comments and suggestions with a view to having an improved version of the Guidance for consideration by the COP-MOP at its eighth meeting.

2. While revising and improving the Guidance, an attempt should be made to take into account the topics prioritized by the AHTEG, on the basis of the needs indicated by the Parties with a view to moving towards operational objectives 1.3 and 1.4 of the Strategic Plan and its outcomes, for the development of further guidance.

3. The AHTEG shall continue to operate the mechanism for regularly updating the list of background documents to the Guidance as established in decision BS-VI/12, paragraph 6, and improved as per paragraph 10 of this decision.

4. Subject to the availability of funds, the Ad Hoc Technical Expert Group on Risk Assessment and Risk Management shall meet face-to-face, at least once, prior to the eighth meeting of the Conference of the Parties serving as the meeting of the Parties to the Protocol.

Expected outcome

5. An improved version of the Guidance on Risk Assessment of Living Modified Organisms.

Reporting

6. The Online Forum and the Ad Hoc Technical Expert Group on Risk Assessment and Risk Management shall submit their reports detailing the activities, outcomes and recommendations for consideration by the eighth meeting of the Conference of the Parties serving as the meeting of the Parties to the Protocol.

MOP-7 Cartagena Protocol on Biosafety (BSP)

South Korea, Sep 29 to Oct 03, 2014[i]

The BSP is a multilateral environmental agreement that under the UN Convention on Biological Diversity contributes to the conservation and sustainable use of biological diversity by ensuring safe transboundary movements of living modified organisms (LMOs). Canada signed the BSP in April 2001 but has not ratified it

The Candel at the MOP-7 was led by Angela Bilkhu (AAFC) and Phil Macdonald (CFIA). As observers, the Candel maintained a low profile at the meeting In general, the tone of the discussion and results obtained at MOP-7 showed a more balanced approach to addressing the environmental safety and trade of LMOs.

Provision (Art)	Objective	What was accomplished / Candel interventions	To watch / To do
Handling, transport, packaging and identification (HTPI) of living modified organisms (LMOs) (Art 18.2.a & 18.3)	Influence a MOP decision to ensure that **(a)** future review of the need for a stand-alone document regarding information requirements under article 18.2.a is no longer warranted and **(b)** existing international standard-setting bodies are adequate to address biosafety considerations pertaining the safe transfer, handling and use of LMOs in the context of Article 18.3	**(a)** A lively discussion about the need for a standalone document to accompany shipments of LMOs intended for direct use as food, feed or for processing (FFPs) resulted in compromise text, suggested by the EU, stating that **further review of the need for a stand-alone document is not required**, unless a subsequent MOP decides otherwise in light of the experience gained. Candel intervened as follows: *As this is the first time Canada is taking the floor, we would like to thank the Republic of Korea for hosting this meeting and the hospitality they have extended to all delegates. Canada would like to remind delegates that scope of Article 18 is limited to LMOs for direct use as food or feed or for processing and does not include in its scope LMOs for environmental release. In Canada's view, the commercial invoice is an example of a well-known document, familiar to industry and easily recognizable and is an appropriate document to put the information required under Article 18.2(a). I would like to support interventions made by South Africa and Ecuador that additional documentation could hamper trade. Consequently, it is Canada's view that there is no need for a standalone document and discussion in regards to this is no longer warranted.*	
		(b) Discussion about HTPI standards was non-controversial. **Parties recognized that the BSP is not a standard-setting body** and agreed that duplication of work should be avoided.	N/A
Risk assessment and risk management (RA/RM; Arts 15 & 16)	Influence a MOP decision to avoid endorsement of the guidance on RA/RM and request that comments received from international experts are incorporated into the document to improve its quality.	Discussion was extensive and heated. As a result, **the proposal to endorse the guidance was removed from the final text. In addition, a recommendation was made to accept the comments received during the review process to improve the quality of the guidance**. Parties also decided to extend the Online Forum and the Ad-Hoc Technical Expert Group (AHTEG), revising its terms of reference and expanding its composition by including one new member from each region with sufficient experience on RA.	

Socio-economic considerations (SEC; Art 26)	Influence a MOP decision to prevent that the AHTEG on SEC is charged with work on guidance that could result in discriminatory measures not based on science to like products that can contradict obligations under the WTO	Discussion was contentious. Several Parties noted that conceptual clarity was not achieved and consequently, a step-wise approach is required. others, proposed that SEC need to include potential benefits. **The AHTEG was extended, subject to the availability of funds, to further develop conceptual clarity on SEC**. The Secretariat will convene online work to review certain topics including international obligations that may be relevant to SEC. A study on international agreements that may have relevance to SEC was also commissioned, pending availability of funds. The AHTEG was charged to develop an outline, to be considered at MOP-8, to start work on guidance as soon as consensus is reached regarding conceptual clarity on SEC.	
Unintentional transboundary movements (UTM) and emergency measures (Art 17)	Influence a MOP decision to avoid reference to Low Level Presence (LLP) and to defer further work on detection and identification, as it relates to UTM of LMOs, unless a clear link is made between detection capacity and the ability to comply with obligations under this article	**LLP was not mentioned** during the discussion or at any point during MOP-7. Early on it was made clear the little understanding Parties have about the difference between UTM and illegal movements (IM). Emphasis on detection and identification as well as the need to include proprietary information for notification purposes (Art 8), among other issues, were subject of intense discussion. At its 13th meeting, the Compliance Committee will consider a compilation of comments by countries to clarify the difference between UTM and IM. Candel interventions were as follows: ***(On Day 1)*** *Canada supports Brazil's intervention. As the EU, Canada is, also, of the view that further work on detection and identification of LMOs under Article 17 should be deferred until a clear link is made between detection capacity and the ability to comply with obligations under this article. Finally, Canada believes that priority should be given to improving risk assessment capacity as this is essential to respond to any outcomes of testing.* ***(On Day 2)*** *Canada would like to support interventions made by Brazil and Argentina. Canada is of the view that the current language that does not contain a prescriptive list will provide parties with more flexibility in determining what information is necessary.*	
Contained use of living modified organisms (Art 6)	Influence a MOP decision to ensure that further work on contained use of LMOs, including the development of tools and guidance, is not considered	Discussion around contained use was mostly non-contentious. Several parties indicated that contained used is out of the scope of the Protocol and others affirmed that this topic was well covered by national standards. **There was agreement to share information on how Parties and other countries regulate contained use of LMO**. Information will be compiled and presented at MOP-8, including any specific requirement relating to the type and level of containment, to determine if gaps exist.	

COP-12 CONVENTION ON BIOLOGICAL DIVERSITY (CBD)

South Korea, Sep 06 to 17, 2014[ii]

Synthetic biology (SB) is a range of new genetic engineering techniques, including the relatively new ability to synthesize long pieces of DNA from chemicals, as well as improved methods for genetic manipulation and design of genetic pathways to achieve more precise control of biological systems. Parties at COP-12 discussed the potential impact of SB on biodiversity as well as possible gaps and overlaps with the Convention and the Cartagena Protocol on Biosafety.

Issue	Objective	What was accomplished / Candel interventions	To watch / To do
Synthetic biology (SB)	To seek that a distinction be made between LMO produced by conventional recombinant DNA technology and new products or processes derived through SB, and to oppose a moratorium on the development of such novel organisms, products and processes that use SB	Canada emphasized the need to apply the precautionary approach to address SB and supported establishing an AHTEG on this topic. In its final decision, **Parties did not considered a moratorium on SB** and agreed that there is currently insufficient information available to decide whether or not this is a new and emerging issue related to biodiversity. Parties also decided to take a precautionary approach and establish, or have in place, effective risk assessment and management procedures and/or regulatory systems to regulate environmental release of any organisms, components or products resulting from SB. Pending funding is available, an AHTEG was formed to continue work on this topic and develop an operational definition of SB including its potential benefits and risks. The AHTEG will also identify the similarities and differences between LMOs as defined in the BSP and SB products to determine if LMOs derived from synthetic biology fall under the scope of the BSP.	

[i] http://www.cbd.int/mop7/
[ii] http://www.cbd.int/cop12/

Heather Shearer - FYI - NABC 26 report - Regulatory trigger and Gene Editing Technologies - Heather Shearer

From: Heather Shearer
To: Annie Savoie; Edward Harrison; John de Jong; Martine de Graaff; Nata...
Date: 2014-11-26 11:38 AM
Subject: FYI - NABC 26 report - Regulatory trigger and Gene Editing Technologies - Heather Shearer
Attachments: CFIA_ACIA - #6048241 - v5 - PBO - NABC 26 report - Regulatory trigger and Gene Editing Technologies - Heather Shearer.DOCX; CFIA_ACIA_-_#6048241_-_vR_-_PBO_-_NABC_26_report_-_Regulatory_trigger_and_Gene_Editing_Technologies_-_Heather_Shearer.DOCX.DRF

Hi everyone,

The attached RDIMS/copy is a draft of my presentation report from the recent National Agricutural Biotechnology Council (NABC) meeting.(http://nabc.cals.cornell.edu/NABC26/Program.html)

These reports essentially summarize the speakers' presentations, and they will be published by the NABC as a record of the meeting. My presentation was an overview of the Canadian regulatory system, with a bit of careful speculation on how gene editing technologies could be handled, since gene editing was the theme of the conference.

I'm sending this up to my Director now for her review, and am sharing this as an FYI, so no need to take action. However, if you have any comments on the content, I'd be pleased to hear them, although I'm hoping to be able to send this to the meeting organizers once Darlene is prepared to proceed, so comments sooner rather than later would be appreciated (or at least flag for me that you'd like for me to hold it).

Best wishes,

Heather

Regulation of Plants with Novel Traits: Canadian Perspectives on the "Novelty" Trigger

Heather Shearer
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Canadian Food Inspection Agency
Ottawa, Ontario

Heather.Shearer@inspection.gc.ca

In determining whether a plant that is the product of gene editing would be regulated in Canada, it is important to consider whether the product would be considered to be novel. The following discussion will focus on Canada's product-based approach to assessing the safety of novel plants for use as food, as feed, and for release into the Canadian environment. As the author works in the area of environmental release of plant with novel traits (PNTs), this will be the main emphasis.

Background Information on the Canadian Regulatory Authorities with Regard to Novel Products of Biotechnology

Canada's product-focused system for regulating agricultural products of biotechnology relies on the use of science-based safety assessments and risk management, with the overall goal of protecting human and animal health as well as the environment. This product-focused framework employs regulatory triggers to distinguish PNTs and novel foods and livestock feeds from their conventional counterparts.

CEPA (*Canadian Environmental Protection Act*) requires that any person who wishes to import, manufacture, or sell any new substance must notify the appropriate Canadian regulatory authority, so that the new substance can be evaluated for potential effects on the environment and human health. To avoid duplication of regulatory oversight, CEPA exempts those products of biotechnology regulated under certain other acts and regulations (e.g. *Seeds Act, Feeds Act, Food and Drugs Act, Fertilizers Act*) from the requirement to notify Environment Canada. However, Environment Canada retains residual powers under CEPA to regulate any products or end uses that other acts do not regulate.

Each act describes the powers held by the Minister responsible for that act. Regulations are made under the authority of the enabling act, and define the application and enforcement of that act. For example, in the case of the *Seeds Act*, the responsible Minister is the Minister of Agriculture and Agri-Food. The Minister's authority to authorize the environmental release of seed is defined in the *Seeds Regulations*, Part V, paragraph 111. To paraphrase, after receiving and assessing all requisite information, and with consideration of risk to the environment, the Minister will authorize release, imposing any conditions necessary to manage environmental risk. Refusing to authorize a release is within the Minister's power only when the proposed release poses an unacceptable risk to the environment, or when the Minister has reasonable grounds to believe the proponent will not respect the conditions imposed upon the release.

To provide guidance in the interpretation of the relevant acts and regulations, departmental documents, such as Directives and Guidelines, are often available. These documents are based on the legislation, but do not have the force of law.

Steps in the Regulatory Process in Canada

Regulatory Trigger

Canada takes a product-based rather than a process-based approach to regulation of biotechnology. The trigger for regulation in all cases is based on novelty. The responsibility to identify that a product may be novel rests with the proponent, while the final decision on novelty rests with the appropriate Canadian regulatory authority. A proponent may be unsure whether a product would be considered 'novel'. In these cases, a consultation with regulators to determine novelty is often a useful step. A full description of this process can be found here: http://www.inspection.gc.ca/plants/plants-with-novel-traits/applicants/pre-submission-consultation/eng/1368394145255/1368394206548

In brief, a novelty determination can involve a meeting between the proponent and regulators from Health Canada and CFIA. The proponent will provide a description of the product. After evaluating the information provided, each regulatory authority will provide the proponent with their novelty determination.

The regulatory trigger is not identical for novel foods, novel feeds, and plants with novel traits. It is therefore necessary to consider whether a product may be novel under each relevant set of regulations:

- *Food and Drugs Act* and *Regulations*: Health Canada
  More information on the assessment and regulation of novel foods can be found at: http://www.hc-sc.gc.ca/fn-an/legislation/guide-ld/nf-an/guidelines-lignesdirectrices-eng.php

Definition of Novel Food from the *Food and Drugs Regulations*:
"novel food"
"novel food" means
(*a*) a substance, including a microorganism, that does not have a history of safe use as a food;
(*b*) a food that has been manufactured, prepared, preserved or packaged by a process that
(i) has not been previously applied to that food, and
(ii) causes the food to undergo a major change; and
(*c*) a food that is derived from a plant, animal or microorganism that has been genetically modified such that
(i) the plant, animal or microorganism exhibits characteristics that were not previously observed in that plant, animal or microorganism,
(ii) the plant, animal or microorganism no longer exhibits characteristics that were previously observed in that plant, animal or microorganism, or
(iii) one or more characteristics of the plant, animal or microorganism no longer fall within the anticipated range for that plant, animal or microorganism.
"genetically modify"
"genetically modify" means to change the heritable traits of a plant, animal or microorganism by means of intentional manipulation.
"major change"
"major change" means, in respect of a food, a change in the food that, based on the manufacturer's experience or generally accepted nutritional or food science theory, places the modified food outside the accepted limits of natural variations for that food with regard to
(*a*) the composition, structure or nutritional quality of the food or its generally recognized physiological effects;
(*b*) the manner in which the food is metabolized in the body; or
(*c*) the microbiological safety, the chemical safety or the safe use of the food.

- *Feeds Act* and *Regulations*: CFIA Animal Feed Division (AFD)
CFIA provides more information on the regulation of novel feeds at:
http://www.inspection.gc.ca/animals/feeds/novel-feeds/eng/1370227088259/1370227136675

Definition of Novel Feed from the *Feeds Regulations*:
"novel trait", in respect of a feed, means a characteristic of the feed that
(*a*) has been intentionally selected, created or introduced into the feed through a specific genetic change, and
(*b*) based on valid scientific rationale, is not substantially equivalent, in terms of its specific use and safety both for the environment and for human and animal health, to any characteristic of a similar feed that is set out in Schedule IV or V

Novelty determination guidance for feed is provided at:
http://www.inspection.gc.ca/animals/feeds/regulatory-guidance/rg-1/chapter-2/eng/1329298059609/1329298179464?chap=6#s25c6

- *Seeds Act* and *Regulations*: CFIA Plant Biosafety Office (PBO) and Plant Biotechnology Risk Assessment Unit (PBRA)
These two groups work closely to manage the environmental release of plants with novel traits (PNTs). PBO is responsible for decision making surrounding novelty and

authorizations of PNTs, and for establishing and implementing policy and programs for PNTs. PBO operates based on the science advice of the risk assessors in PBRA. For more information on the regulation of the environmental release of plants with novel traits, visit:
http://www.inspection.gc.ca/plants/plants-with-novel-traits/eng/1300137887237/1300137939635

Definition of Novel Trait from the *Seeds Regulations*:
"novel trait", in respect of seed, means a characteristic of the seed that
(*a*) has been intentionally selected, created or introduced into a distinct, stable population of cultivated seed of the same species through a specific genetic change, and
(*b*) based on valid scientific rationale, is not substantially equivalent, in terms of its specific use and safety both for the environment and for human health, to any characteristic of a distinct, stable population of cultivated seed of the same species in Canada, having regard to weediness potential, gene flow, plant pest potential, impact on non-target organisms and impact on biodiversity

To provide proponents with additional guidance on the determination of novelty, PBO provides Directive 2009-09: *Plants with novel traits regulated under Part V of the Seeds Regulations: Guidelines for determining when to notify the CFIA*
http://www.inspection.gc.ca/plants/plants-with-novel-traits/applicants/directive-2009-09/eng/1304466419931/1304466812439

Regulatory Trigger: Special Cases

1) *A product does not trigger all three regulatory authorities:* Not all products will trigger regulation as novel foods, novel feeds, and for environmental release. For example, a herbicide resistant turfgrass would not be expected to trigger regulation as a novel food if the turf species is not used as food. Similarly, a virus-resistant citrus cultivar would not be considered to be a PNT in Canada if the crop is not capable of surviving in this climate, even though approval for use as food and feed would still be required. When a novel product triggers the requirement for regulatory approval under more than one legislation, under Canada's "no split approvals" policy, it will be authorized only once all implicated regulatory authorities are prepared to proceed.

2) *Retransformation/remutation:* It is worth noting that, in certain cases, even if regulation is triggered, a full risk assessment may not be required by all three assessment groups (novel foods, novel feeds, and environmental release). One example of this is "retransformation". For the purposes of environmental release, retransformation is defined as the transformation of a plant with a DNA construct that has already been authorized in another variety of that species, provided that the intended uses are similar, and that the plant is known to be similar to the authorized PNT (for more details, consult CFIA Directive 94-08). A related policy applies to remutation events. This is particularly relevant to vegetatively-propagated crops such as potato, where incorporating a novel trait into varieties through conventional breeding methods is impractical.

In these cases, the plant is still considered to be novel, and is therefore subject to the same regulatory requirements as the original event. However, since a risk assessment would not be required, its authorization for environmental release could be greatly simplified. In principle, this concept would be equally applicable to some products of gene editing technologies, although, with no formal policy in place at the time of this writing, consultation with regulatory authorities is encouraged early in the development process. As well, please note that, since Canada is a Codex signatory, Health Canada adheres to international guidance regarding recombinant DNA technologies, and may therefore differ from CFIA in decisions on whether assessment of re-transformation events is required.

A history of use in Canada: Part V of the *Seeds Regulations* was drafted in such a manner that it grandfathered in potentially novel products of biotechnology that had already been released into the Canadian environment prior to its enactment. This means that, if a crop and trait was present in Canadian agriculture prior to 1996, it would not be considered to be a PNT. However, food or feed products derived from plants with an historic use exemption under the *Seeds Regulations* would not necessarily be exempt under the *Food and Drugs Regulations* or *Feeds Regulations*.

Comment [HS1]: For food and feed colleagues... is there anything you'd like to add to this section on historic use exemptions? I don't know how you handle such products, so I basically just left your programs out of this discussion

If this Part V exemption had not been implemented, many products that fall within the "novel" category would have required assessment even though they may have already been safely grown for many years in Canada. Some examples of such products include triticale (which was first released in Canada in 1969), canola (since it was not substantially equivalent to rapeseed), and triazine tolerant canola (since it displayed a novel herbicide tolerance).

Similarly, this concept of "new to Canada" continues to apply in novelty assessments today. If a proponent can demonstrate that a trait was already present in that species in Canadian agriculture prior to 1996, then the trait is not novel for the purpose of environmental release. For example, if a plum cultivar with resistance to plum pox virus had been cultivated in Canada prior to 1996, the genome of a different cultivar could be modified using gene editing techniques to possess the same sequences and demonstrate the same resistance. Since the trait is not new to the species, a reasonable case could be made in some situations that this is not a PNT.

Pre-Submission Consultation

A pre-submission consultation is available to proponents who wish to discuss their products with regulators prior to making a submission. Pre-submission consultation provides the proponent with an opportunity to present an overview of their submission and ask specific questions regarding the content of their submission. Assessors will provide guidance on the information requirements specific to the individual product, explain regulatory requirements, and clarify expectations for data quality.

This practice often reduces the number of requests from regulator(s) for either clarification or additional information that might otherwise have been required in order to complete a safety

assessment and reach a decision. Health Canada (HC) and the CFIA have developed a guidance document for pre-submission consultation that is intended to provide new applicants with more information. It is available at:
http://www.inspection.gc.ca/plants/plants-with-novel-traits/applicants/pre-submission-consultation/eng/1368394145255/1368394206548

Data Submission and Review

Where a safety assessment is required, the proponent must make applications to satisfy the data requirements of each regulatory group. In the case of novel foods, evaluators will perform a nutritional assessment and toxicology assessment (which considers the chemical, toxicological, and allergenicity of the novel food) to determine whether the novel product is equivalent to its conventional counterpart, as well as a molecular characterization of the genetic change. The novel feed assessment performed by AFD also includes nutrition, toxicology, and molecular reviews, but considers this information in the distinct context of use as feed. With respect to environmental safety, evaluators perform a molecular characterization, and assess the PNT against its conventional counterparts by reviewing information addressing: weediness, gene flow, plant pest potential, impacts on non-target organisms, and impacts on biodiversity. There are many similarities in these reviews (for example, all three groups perform a molecular characterization); in recognition of this, evaluators are in regular communication with each other to maximize efficiency.

If, following a review of all submitted information, the evaluators have questions or require clarification of information submitted, a letter will be sent directly to the proponent outlining these questions and/or requests for clarification. Information requirements have been met once any outstanding requests for further information and/or clarification have been satisfied. At this point, the science review is complete, and the regulatory decision will be made.

Regulatory Decision

When a plant is considered to be a PNT and a source of a novel food and a novel feed, regulatory decisions regarding the use as a novel feed, novel food and environmental release will be coordinated and harmonized to minimize the potential for unapproved products to enter the Canadian environment or food or feed supplies. Once regulatory decisions have been harmonized, the CFIA and HC will send decision letters to the proponent and post a decision document on their respective websites. The decision document summarizes the information that was assessed, and the evaluators' findings.

Furthermore, risk management of certain PNTs may be required as a condition of authorization. Risk management imposes requirements on the use of the PNT such that identified potential risks to the environment are mitigated. Risk management may not be necessary or appropriate for all PNTs, but some PNTs (particularly insect-resistant and herbicide-tolerant PNTs) warrant a stewardship plan.

Considerations that may Impact Future Policy Development Relating to the Environmental Release of Products of Gene Editing

Advancements in molecular analysis techniques continue to contribute to our understanding of plant genomes and genetic change. As well, after nearly two decades with novel plant products available in the marketplace, a high degree of familiarity with these products has developed. In keeping with the comparative approach that Canada takes to assessing the novel products, risk assessors from CFIA and Health Canada undertook a literature review to compare the insertional effects that could arise during the creation of a PNT to other types of spontaneously-occurring genetic changes in plants (Schnell *et al.*, 2014). The findings of this review will help to inform future policy direction to help ensure that regulators are focusing their efforts in assessing novel products of biotechnology in a manner that is suited to the expected potential for risk.

The product-based approach to regulation allows the Canadian regulatory system to effectively adjust to any new developments in the science of plant breeding. Policy work is ongoing to help ensure that guidance documents are available as products of gene editing are brought forward for assessment. CFIA and Health Canada are committed to providing an efficient and appropriate level of regulatory oversight that encourages innovation while allowing Canadians to benefit from the advances brought by new technologies.

Reference

Schnell J Steele M Bean J Neuspiel M Girard C Dormann N Pearson C Savoie A Bourbonnière L Macdonald P (2014) A comparative analysis of insertional effects in genetically engineered plants: considerations for pre-market assessments. Transgenic Research, in press

s.19(1)

From: Nataliya Dormann
To: Barnola, Luis
CC: Jim.Louter@ec.gc.ca; John.Moffet@ec.gc.ca
Date: 2014-11-27 2:40 PM
Subject: Re: Confirmation of nominations of experts for participation in the Open-ended Online Expert Forum on Risk Assessment and Risk Management

She found it:)
Promised to approve it sometimes middle of the next week.

Thank you all,
Nataliya

>>> "Barnola, Luis" <Luis.Barnola@AGR.GC.CA> 2014-11-27 12:30 PM >>>
Nataliya, you may want to respond directly to and clarify that both profiles are already uploaded in the BCH.

Many thanks!
LB
Luis Barnola/MISB/TAND/TTPD
Sent from my BlackBerry

From:
Sent: Thursday, November 27, 2014 12:25 PM
To: Canada - Mr. John Moffet <john.moffet@ec.gc.ca>
Cc: BCH Records; Barnola, Luis; Roussel-Bedard,Tina [NCR] <Tina.Roussel-Bedard@ec.gc.ca>; Lafontaine,Lynn [NCR] <Lynn.Lafontaine@ec.gc.ca>; Phil Macdonald <philip.macdonald@inspection.gc.ca>; Jim Louter <jim.louter@ec.gc.ca>; Colin McGowan <colin.mcgowan@dfo-mpo.gc.ca>
Subject: RE: Confirmation of nominations of experts for participation in the Open-ended Online Expert Forum on Risk Assessment and Risk Management

Dear Mr. Moffet,
Thank you for your response on the matter. The confirmed and new nominations are duly noted. The list of Canadian nominees will be updated shortly.

Please note, I have yet to receive the uploaded profile for Dr. James (Jim) Louter.

Furthermore I would greatly appreciate it of Dr. Philip Macdonald can review his expert profile http://bch.cbd.int/database/record.shtml?documentID=100018 and ensure the information is complete and up to date.

Best regards,

From: Moffet,John [NCR] [mailto:John.Moffet@ec.gc.ca]
Sent: November-27-14 12:10 PM
To:
Cc: Canada - Ms. Nataliya Dormann; Luis Barnola; Roussel-Bedard,Tina [NCR]; Lafontaine,Lynn [NCR]; secretariat; Phil Macdonald; Jim Louter; Colin McGowan
Subject: Re: Confirmation of nominations of experts for participation in the Open-ended Online Expert Forum on Risk Assessment and Risk Management

Biosafety Division, Secretariat of the CBD

Dear

As the Government of Canada's Focal Point for the Cartagena Protocol on Biosafety, I wish to notify you that Canada continues to support the participation of Dr. Philip Macdonald (1) in the risk assessment open-ended online expert forum and the respective Ad Hoc Technical Expert Group.

In addition, Canada would like to nominate Dr. Jim Louter (2) and Dr. Colin McGowan (3) to participate in the risk assessment open-ended online expert forum.

As per the Secretariat's request, profiles for these nominees have been uploaded to the Biosafety Clearinghouse for your consideration and approval.

(1) Dr. Philip Macdonald
National Manager, Plant and Biotechnology Risk Assessment Unit
Canadian Food Inspection Agency
1400 Merivale Road, Tower 1, 1-242
Ottawa, Ontario K1A 0Y9
Canada
T: (613) 773-5288
F: (613) 773-5391
philip.macdonald@inspection.gc.ca
http://bch.cbd.int/database/record.shtml?documentID=100018

(2) Dr. James (Jim) Louter
Manager, Biotechnology Section
Environment Canada
200 Sacre Coeur, Fontaine Bldg, 9th floor,
Gatineau, Quebec K1A 0H3
Canada
T: (819) 938-3348
F: (819) 994-3121
jim.louter@ec.gc.ca

(3) Dr. Colin McGowan
Science Advisor, Aquaculture, Biotechnology and Aquatic Animal Health Science Branch
Department of Fisheries and Oceans
200 Kent Street
Ottawa, Ontario K1A 0E6
Canada
T: (613) 990-7033
F: (613) 991-1378
Colin.McGowan@dfo-mpo.gc.ca

Please let me know if the Secretariat requires additional information about the above mentioned experts.

Sincerely,

John Moffet

Director General, Legislative and Regulatory Affairs, Environment Stewardship Branch
Environment Canada / Government of Canada
john.moffet@ec.gc.ca / 819-420-7907

Directeur général, Affaires législatives et réglementaires, Direction générale de l'intendance

s.19(1)

environnementale
Environnement Canada / Gouvernement du Canada
john.moffet@ec.gc.ca / 819-420-7907

From:
Sent: Wednesday, November 26, 2014 05:18 PM
To: Moffet,John [NCR]
Cc: Canada - Ms. Nataliya Dormann <bchrecords@inspection.gc.ca>
Subject: Confirmation of nominations of experts for participation in the Open-ended Online Expert Forum on Risk Assessment and Risk Management

Dear Mr. John Moffet,
In following up on my previous correspondence (below) on the nomination of experts to the Open-ended Online Expert Forum on Risk Assessment and Risk Management under the Cartagena Protocol on Biosafety, I would like to remind you that the deadline for receiving nominations is the 30th November 2014. If you have any questions or require any assistance with the nomination process please do not hesitate to contact us at any time.
Best regards,

Biosafety Division

Secretariat of the Convention on Biological Diversity
United Nations Environment Programme
413 Saint Jacques, suite 800
Montreal, QC, H2Y 1N9
Canada

Tel: +
Fax: +1-514-288-6588
Web: www.cbd.int<http://www.cbd.int>

Dear Mr. John Moffet,

In its decision BS-VII/12, paragraph 8, the COP-MOP invited Parties, other Governments and organizations to confirm the nominations of their experts who are currently participating in the Open-ended Online Expert Forum on Risk Assessment and Risk Management (http://bch.cbd.int/onlineconferences/forum_ra.shtml), and requested the Executive Secretary to remove the records of experts whose nominations have not been confirmed.

Further to this decision, the Secretariat issued notification SCBD/BS/MPM/DA/83988 (attached) on 28 October 2014 inviting Focal Points to take the appropriate steps with the view to implementing this element of the decision.

In order to facilitate the process, we have compiled, for your convenience, the names of the experts from your country who are currently registered as participants in the Online Forum. The experts are:

1. Dr. Robert Devlin Fisheries and Oceans Canada (DFO)

2. Mr. Philip Macdonald Canadian Food Inspection Agency (CFIA)

s.19(1)

3. Dr. Desmond Mahon Environment Canada (EC)

4. Dr. Arash Shahsavarani Government of Canada

We would appreciate if you could confirm which experts, from the list above, continue to be supported for participation in the Open-ended Online Expert Forum on Risk Assessment and Risk Management.

The confirmation of experts is to be done as soon as possible but no later than 30 November 2014 either by replying to this email or via correspondence to secretariat@cbd.int<mailto:secretariat@cbd.int>. The records of experts who are not confirmed will be removed from the Online Forum as requested by the COP-MOP soon after the deadline.

Furthermore, nominations for new experts to the Online Forum continue to be accepted on an ongoing basis. Information on how to nominate new experts to the Online Forum can be found in the attached notification.

Best regards,

Biosafety Division

Secretariat of the Convention on Biological Diversity
United Nations Environment Programme
413 Saint Jacques, suite 800
Montreal, QC, H2Y 1N9
Canada

Tel: +
Fax: +1-514-288-6588
Web: www.cbd.int<http://www.cbd.int>

[Image removed by sender. International Day for Biological Diversity 2014]<http://www.cbd.int/idb/2014/>

[International Day for Biological Diversity 2014] <http://www.cbd.int/idb/2014/>

Edward Harrison - Placeholder: Heather Shearer's Gene-editing Talk for the CFIA-HC Joint Seminar Series

From: Sarah G. Davis
To: Bean, Jordan; Biotech Team; Boadi, Dinah; Bourbonniere, Luc; Chen, C...
Date: 2015-01-21
Time: 1:00 PM - 4:00 PM
Subject: Placeholder: Heather Shearer's Gene-editing Talk for the CFIA-HC Joint Seminar Series
Place: Banting auditorium for part 1, B306 Banting
CC: Kehoe, Amy

Please delegate as appropriate. I tried to include as many people from PBRA, PBO, AFD and HC as possible, but I've definitely missed some. Please review the list of addressees on this appointment and delegate within your group as needed.

Hi all,

I wanted to send this appointment as a placeholder in your calendars. On January 21st, Heather Shearer will be delivering a presentation on the topic of targeted gene-editing techniques (an abstract with further details has been provided below). This presentation is set to occur from 1:00-2:00 pm in the Banting auditorium at Tunney's Pasture. For your information, Heather's presentation is being co-organized by the CFIA's Plant Research Seminar Series (by Amy Kehoe) and Health Canada's Food Directorate Seminar Series (by Christina Clarke). I expect you may receive a formal invitation via one of these two avenues in the coming weeks.

Immediately after Heather's talk, regulators from PBRA, PBO, AFD and HC are invited to stay for a roundtable discussion, similar to what was organized after Michele McMillan's RNAi presentation. This discussion is set to take place from approximately 2:15-4:00 pm in room B306 of the Banting Building (although it may finish earlier). For those that would like to participate in the roundtable discussion via teleconference, please use the following call-in information:

Phone number: 613-960-7516*
Conference ID:

*Please note that this conference line is a different line than what will be used during Heather's presentation. Those call-in details will be given in the appointment by the CFIA's Plant Research Seminar Series/HC's Food Directorate Seminar Series.

Sincerely,
Sarah

Targeted Gene-Editing Techniques: A New Horizon in Genome Customization

First, there was domestication, then, selective breeding. In the 20th century, we got inventive with atomic gardens, cloned animals, and crossed the species barrier using recombinant DNA techniques. The newest innovation in agricultural biotechnology has now arrived: targeted gene editing.

Gene editing techniques allow a genome to be precisely modified. Using customized engineered enzymes and

synthesized nucleotide templates, it is now possible to "re-write" a specific gene sequence. For example, a single genetic locus controls whether cattle have horns. By editing only a few nucleotides in horned dairy cattle to be more like hornless beef cattle, a hornless trait could be introduced into the dairy breed, without changing any other breed characteristic. Beyond tweaking existing genes, gene editing techniques also allow the introduction of longer stretches of entirely new synthetic sequence, or can be used to excise a sequence from the genome. Genes can be moved from one chromosome to another, which simplifies conventional breeding by physically linking groups of desirable traits. "Landing pad" sites on a chromosome that allow optimal gene expression can be created and used to insert multiple new gene sequences at precise locations.

This presentation will provide basic details on the molecular biology of the CRISPR/Cas9, TALEN, and zinc-finger nuclease enzymes that make gene editing possible, and will discuss the kinds of genetic changes that can be envisioned.

With the rapid uptake and ease of use of these technologies, it is likely that products of gene editing will be submitted for pre-market assessment in the near future. For regulators, these techniques could pose some interesting challenges. Has something new been introduced if a genome has been rearranged? Is a novel trait present when a gene has been re-written to resemble another existing breed or variety? How does the use of a "landing pad" site relate to our understanding of recombinant DNA techniques, stacked products, and insertional effects? Are off-target mutations a concern, and how can they be detected? It is hoped that this presentation will spark further discussion of these and other science and policy questions relating to targeted gene editing.

s.19(1)

From: Nicole van der Lee
To: Davis, Sarah G.; Schnell, Jaimie
Date: 2015-02-23 9:43 AM
Subject: Fwd: Simplot responses to combined HC/CFIA letter dated August 27, 2014
Attachments: final CFIA-HC response 23Feb15.doc

FYI

>>> 2015-02-20 7:04 PM >>>

Attached please find Simplot's response to the combined CFIA/HC letter dated August 27, 2014, regarding questions for the E12, F10, J3 and J55 potato events with low acrylamide potential and reduced black spot bruising (submission file # 4000310).

On Monday I will overnight each of you a signed hard copy of this response, including a CD with PDFs of all the references cited.

As I explained in the cover letter, I truly apologize for the length of time it has taken us to respond. We intend to be much more prompt in our responses going forward.

Please let us know if you have any questions.

Best regards,

Simplot Plant Sciences
Tel. (
Mobile (

-

Simplot Plant Sciences

J.R. Simplot Company 5369 W Irving St Boise ID 83706

February 23, 2015

Plant and Biotechnology Risk Assessment
Canadian Food Inspection Agency
1400 Merivale Road
Ottawa, Ontario K1A 0Y9
Attention: Nicole van der Lee

Animal Feed Division
Canadian Food Inspection Agency
59 Camelot Drive
Ottawa, Ontario K1A 0Y9
Attention: Marina Steele

Novel Foods Section, Evaluation Division, Bureau of Microbial Hazards
Food Directorate, Health Canada
251 Sir Frederick Banting Driveway, PL 2204E
Ottawa, Ontario K1A 0Y9
Attention: Luc Bourbonnière

Re: J. R. Simplot Company's Low Acrylamide Potential and Reduced Black Spot Bruising Potato Events E12, F10, J3, and J55; Submission File # 4000310

Simplot response to CFIA PBRA, CFIA AFD, and Health Canada questions dated August 27, 2014

Dear Ms. van der Lee, Ms. Steele, and Mr. Bourbonnière:

This letter is in response to your letter of August 27, 2014, requesting additional information regarding the molecular characterization data that was provided in the application.

Please find the responses to your questions on the following pages. I sincerely apologize for the length of time it has taken us to respond. My predecessor, Pete Clark, left Simplot last fall and his position was not filled until I started with the company earlier this month. These Innate™ potato events continue to be important, and we would like to continue with the CFIA and Health Canada review and authorisation process.

s.19(1)

For future reference, here is my contact information:

J.R. Simplot Company
5369 West Irving Street
Boise, ID 83706
Tel:
Mobile:
Fax: (208) 780-6027
Email:

Please do not hesitate to contact me if you have any further questions or concerns.

Sincerely,

cc: Robert Potter Consulting

Table of Contents **Pages**

Responses to Questions

The following points regarding the molecular characterization data require clarification or additional information:

1. **Please provide additional information on the genetic elements introduced into potato events E12, F10, J3, and J55, including a citation where these functional sequences were described, isolated, and characterized; the functions of the genes from which they were derived; and whether the genes from which they were derived encode proteins that are responsible for disease or injury to plants or other organisms or are known toxicants, allergens, pathogenicity factors, or irritants.**

   The origin and citations of sequences were provided in Table 4 Genetic elements of the DNA insert of pSIM1278, from Left Border site to Right Border site (Chapter 2) of the original submission. Additional details, including the functions of the proteins, are provided in ***Supplement A: Molecular Pathways and Characterization***. Importantly, the inserted genetic elements do not code for any proteins.

2. **Please provide detailed descriptions of the proposed modes of action by which the low acrylamide, low black spot bruising, and low reducing sugar traits are introduced into potato event E12, F10, J3, and J55. These proposed modes of action should be based on data or scientific rationale supported by published studies and should specify the roles of the Asn1, Ppo5, Phl, and R1 proteins and identify the substrates, end products, and intermediaries within potato events E12, F10, J3, and J55 that are proposed to be affected by the modification according to the modes of action.**

   Additional information regarding the mode of action for each silencing target is described in ***Supplement A: Molecular Pathways and Characterization***.

3. **Please provide bioinformatics analysis and/or a clear, scientific rationale that supports that, based on sequence specificity, the introduced genetic elements (dsRNA) into potato events E12, F10, J3 and J5 are unlikely to interact with unrelated transcripts in these events, non-target organisms, livestock and humans in a biologically significant or adverse manner.**

The possibility of off-target effects in potatoes are discussed in ***Supplement B: Analysis of pSIM1278 siRNA Targets and Specificity***. Further discussion of exposure and safety risks to other organisms associated with consumption of Innate™ potatoes expressing dsRNA, is provided in ***Supplement C: Safety Considerations for Nucleic Acid, including Double-Stranded RNA and siRNA***.

4. **Please provide (i) an estimated expression level of the dsRNA present in edible tissues of potato events E12, F10, J3 and J55 and (ii) an estimated total dsRNA dietary exposure in livestock and humans, with consideration given to: survival of dsRNA following any processing or cooking that may occur, bioavailability of the ingested dsRNA by livestock and humans, and, estimated consumption levels of the relevant parts of the plant in livestock and humans.**

We have not attempted to estimate the expression level of dsRNA present in edible tissues as there are no meaningful comparisons for those measurements. Humans and other animals ingest large, but unquantifiable amounts, of dsRNA, miRNA, and siRNA as part of their natural diets. Nucleic acids are highly susceptible to degradation in the presence of high temperatures, acidic or alkaline treatment, and proteases. Raw potato material consumed by animals is subjected to acidic and enzymatic digestion. Since consumption of potatoes or processed potatoes generally occurs following cooking, frying, and/or other harsh treatments, the nucleic acid in those products will be highly degraded, including but not limited to dsRNA. This is clearly evident by the fragmented nature of genomic DNA isolated from processed potato products as shown in Figure 1. Under these conditions the majority of genomic DNA is fragmented in small pieces (less than 1 kb) prior to ingestion. Total RNA is more difficult to measure in this way, but is generally less stable than DNA and expected to be even more degraded under these conditions.

Further rationale, including dietary exposure and safety risks associated with consumption of Innate™ potatoes expressing dsRNA, is provided in ***Supplement C: Safety Considerations for Nucleic Acid, including Double-Stranded RNA and siRNA***.

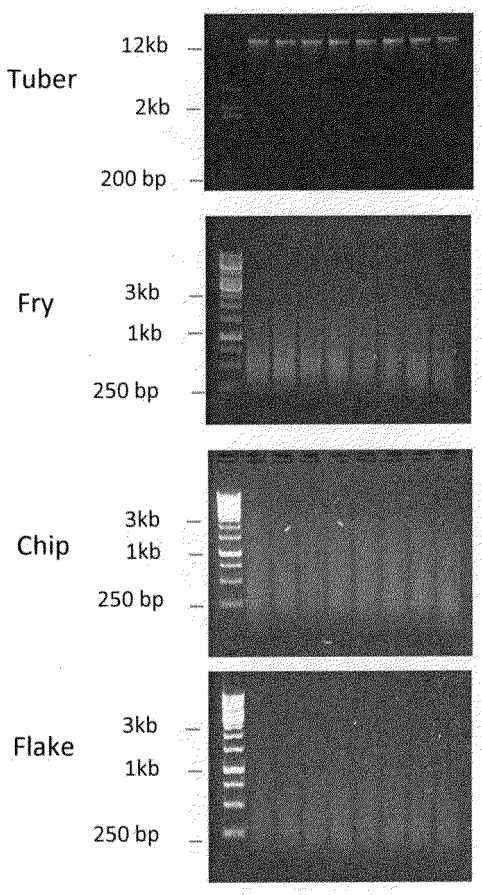


Figure 1. Fragmentation of genomic DNA in processed potato products compared with raw tubers. Genomic DNA was isolated and evaluated on a 1% agarose gel stained with ethidium bromide. Lane 1 contains a molecular weight marker where the following 8 lanes contain independent DNA isolations from the noted raw or processed food material.

5. **Wild potato (*Solanum verrucosum*) is the source of the Ppo5 gene sequence used to generate potato events E12, F10, J3, and J55 but was not characterized in the submission. Please provide the following information regarding wild potatoes: (i) common or usual names; scientific name and taxonomic classification, (ii) a critical assessment of the ability of the organism to produce/contain potentially toxic compounds (e.g., heavy metals, pesticides), anti-nutritional compounds and endogenous allergens, (iii) available toxicology data for the organism, and (iv) information on history of use of the organism, or any related organisms, in food and livestock feed.**

Solanum verrucosum Schlechtd. is a dipoid (2n = 24) wild potato species from Mexico that is fertile and valuable as a source of disease resistance genes for potato breeding (Spooner et al 2014). There are reports of *S verrucosum* tubers being edible and having yellow flesh with a good flavor. All Solanum species contain quantities of alkaloids, including solanine and solanidine.

There is no relationship between the small region of *Ppo5* trailer sequence and the toxicology profile of the donor or host organisms. The DNA transferred into *S. tuberosum* is derived from an untranslated region of the *Ppo5* gene in *S. verrucosum*. This sequence does not serve as a template for protein synthesis in either of the organisms, and its mode of action in the host organism is distinct from the donor organism (e.g. messenger RNA non-coding sequence vs. dsRNA silencing trigger).

S. verrucosum was chosen as the source of trailer sequence primarily for business reasons. As shown in the following alignment (Figure 2), the trailer sequence derived from *S. verrucosum* used in pSIM1278 (1278) is nearly identical (97% identity; ≤ 7 nt mismatches) to the sequences found natively in the commercial varieties. In fact, the extended regions of identity between the introduced sequence and the native sequence accounts for the efficacy in Innate™ potatoes.

Thus, there is no rationale for evaluating the anti-nutritional compounds, allergens, or toxicology data of *S. verrucosum* in relation to Innate™ potatoes.

Reference
DM Spooner, M Ghislain, R Simon, SH Jansky and T Gavrilenko. 2014. Systematics, diversity, genetics, and evolution of wild and cultivated potatoes. Bot. Rev. 80:283-383.

```
RB1             TAGTCTCTATTGAATCTGCTGAGATTACACTTTGATGGATGATGCTCTGTTTTTATTTTC 60
RB2             TAGTCTCTATTGAATCTGCTGAGATTACAGTTTGATGGATGATGCTCTGTTTTTATTTTC 60
RR1             TAGTCTCTATTGAATCTGCTGAGATTACACTTTGATGGATGATGCTCTGTTTTTGTTTTC 60
RR2             TAGTCTCTATTGAATCTGCTGAGATTACACTTTGATGGATGATGCTCTGTTTTTGTTTTC 60
At1             TAGTCTCTATTGAATCTGCTGAGATTACACTTTGATGGATGATGCTCTGTTTTTGTTTTC 60
At2             TAGTCTCTATTGAATCTGCTGAGATTACACTTTGATGGATGATGCTCTGTTTTTATTTTC 60
At3             TAGTCTCTATTGAATCTGCTGAGATTACTGTTTGATGGATGATGCTCTGTTTTTATTTTC 60
Sn1             TAGTCTCTATTGAATCTGCTGAGATTACTGTTTGATGGATGATGCTCTGTTTTTATTTTC 60
Sn2             TAGTCTCTATTGAATCTGCTGAGATTACACTTTGATGGATGATGCTCTGTTTTTGTTTTC 60
Sn3             TAGTCTCTATTGAATCTGCTGAGATTACACTTTGATGGATGATGCTCTGTTTTTGTTTTC 60
1278            TAGTCTCTATTGAATCTGCTGAGATTACACTTTGATGGATGATGCTCTGTTTTTGTTTTC 60
                ***************************  ************************* *****

RB1             TTGTTCTGTTTTTTCAT--GTTGAAATCAGCTTTGTTGCTTGATTTCATTGAAGTTGTTA 118
RB2             TTGTTCTGTTTTTTCAT--GTTGAAATCAGCTTTGTTGCTTGATTTCATTGAAGTTGTTA 118
RR1             TTGTTCTGTTTTTTCCT--GTTGAAATCAGCTTTGTTGCTTGATTTCATTGAAGTTGTTA 118
RR2             TTGTTCTGTTTTTTCCTCTGTTGAAATCAGCTTTGTTGCTTGATTTCATTGAAGTTGTTA 120
At1             TTGTTCTGTTTTTTCAT--GTTGAAATCAGCTTTGTTGCTTGATTTCATTGAAGTTGTTA 118
At2             TTGTTCTGTTTTTTCAT--GTTGAAATCAGCTTTGTTGCTTGATTTCATTGAAGTTGTTA 118
At3             TTGTTCTGTTTTTTCAT--GTTGAAATCAGCTTTGTTGCTTGATTTCATTGAAGTTGTTA 118
Sn1             TTGTTCTGTTTTTTCAT--GTTGAAATCAGCTTTGTTGCTTGATTTCATTGAAGTTGTTA 118
Sn2             TTGTTCTGTTTTTTCCTCTGTTGAAATCAGCTTTGTTGCTTGATTTCATTGAAGTTGTTA 120
Sn3             TTGTTCTGTTTTTTCAT--GTTGAAATCAGCTTTGTTGCTTGATTTCATTGAAGTTGTTA 118
1278            TTGTTCTGTTTTTTTAT--GTTGAAATCAGCTTTGTTGCTTGATTTCATTGAAGTTGTTA 118
                ************** *  ****************************************

RB1             TTCAAGAATAAATCAGTTACAATTAT 144
RB2             TTCAAGAATAAATCAGTTACAATTAT 144
RR1             TTCAAGAATAAATCAGTTACAATTAT 144
RR2             TTCAAGAATAAATCAGTTACAATTAT 146
At1             TTCAAGAATAAATCAGTTACAATTAT 144
At2             TTCAAGAATAAATCAGTTACAATTAT 144
At3             TTCAAGAATAAATCAGTTACAATTAT 144
Sn1             TTCAAGAATAAATCAGTTACAATTAT 144
Sn2             TTCAAGAATAAATCAGTTACAATTAT 146
Sn3             TTCAAGAATAAATCAGTTACAATTAT 144
1278            TTCAAGAATAAATCAGTTACAATTAT 144
                *************************
```

Figure 2. Alignment of the sequence of *Ppo5* trailer from *S. verrucosum*, which was used in the pSIM1278 silencing cassette (1278), with the trailer sequences found in a number of alleles within the commercial *S. tuberosum* varieties Russet Burbank (RB), Ranger Russet (RR), Atlantic (At), and Snowden (Sn).

6. **The following questions pertain to the Southern blots used to establish the structure and copy number of potato event E12, F10, J3, and J55 (i.e. Figures 10-13, 15-18, 20-23, and 25).**

   a. **There were no positive controls shown on the Southern blots used to establish the structure and copy number of potato event E12, F10, J3, and J55 (i.e. Figures 10-13, 15-18, 20-23, and 25). Please indicate how it was established that the DNA probes were sufficiently sensitive to detect a single copy number of their homologous genetic elements.**

      When T-DNA is inserted into a chromosome a unique junction is naturally created. This junction must exist and can only be present as a single copy. Thus, the presence of these bands ensures we are loading sufficient DNA to detect a single copy with each of our probes. We were able to detect these junction bands in all events.

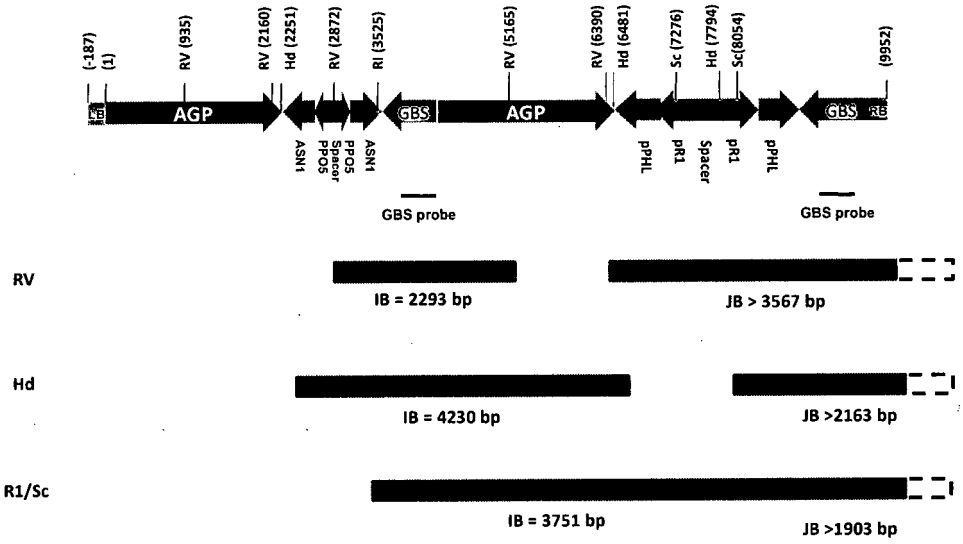
   b. **In the figure describing the probes used to determine copy number and insert structure (i.e. Figure 4), the AGP2 and AGP3 probes appear to be homologous to a large proportion of the Agp promoter, however, results of the binding of these probes were not provided. Please provide these results.**

      The requested Southern blots and analysis supporting our proposed structures are provided in ***Supplement D: Supporting Southern Blot Studies using AGP2 and AGP3 Probes***.

   c. **In the figure representing the expected IB and JB of DNA insert digests hybridized with GBS Probe (i.e., Figure 8), an additional IB of 1313 bp is indicated which would not be recognized by the GBS probe. Please indicate if this represents an error in the figure.**

      As suggested, there is an error in Figure 8 of the original submission associated with the Hd (HindIII) digest. There are only two digestion products detectable by the GBS probes (i.e. those located fragments located directly below the GBS probe in that figure). The "IB =1313 bp" label should not have been included in the figure and can be disregarded. A revised Figure 8 is provided:

Figure 1. Expected IB and JB of DNA Insert Digests Hybridized with GBS Probe (Revised)



d. Lane 3 of The Southern blot of J3 and J55 genomic DNA probed with AGP probe (i.e., Figure 49) is unlabelled. Please indicate what DNA sample is present in this lane.

The label associated with lane 3 was mistakenly omitted. It should have been marked as "wt G0".

e. The sizes of the junction bands indicated in figures displaying the expected IB and JB of DNA insert digests hybridized with ASN, AGP, PHL, and GBS probes (i.e. Figures 5-8) were 5 bp greater than the size of the fragments as calculated using the position of the closest restriction endonuclease site. Please comment on this discrepancy.

The junction between the left border (LB) and the pAGP element consists of a KpnI restriction site (5'...GGTAC↓C...3'), which produces a 5 nt overhang when cutting between the two cytosine residues. The software used to determine the restriction site locations shown in Figure 5 of the original submission was calculating based upon the cut site within KpnI rather than at the start of the KpnI site, which led to a 5 nt offset. This 5 nt region has since been accounted for as shown in the following Figure 3:

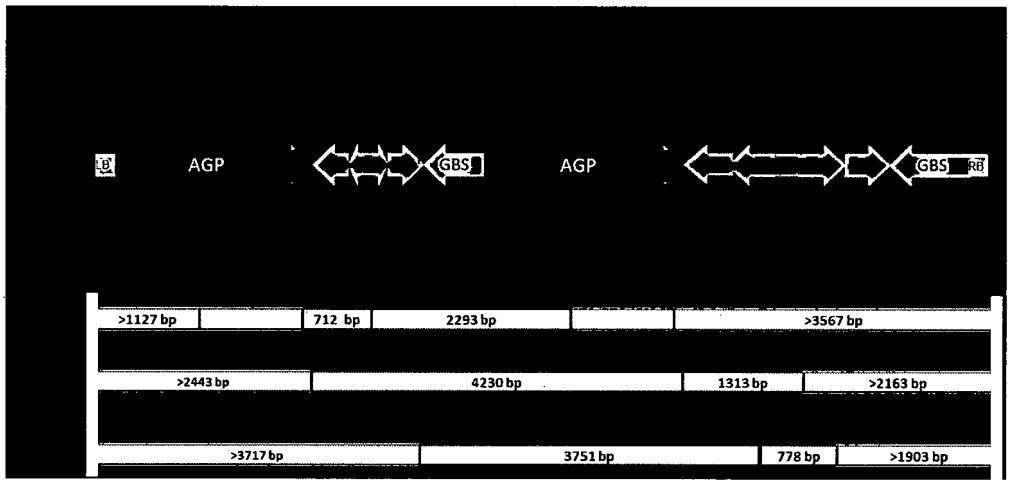


Figure 3. Adjusted structure and coordinate scheme for the pSIM1278 DNA insert.

f. In Southern blots of F10, J3, and J55 DNA probed with AGP (i.e., Figures 36 and 50), some endogenous bands were not consistently detected:

i. In the Southern blot of G0 and G2 F10 DNA probed with AGP (i.e., Figure 36), the endogenous 4.9 and 6.5 kb bands were absent despite the fact that these bands were observed on Southern blots of G0, G1, and G3 F10 DNA samples (i.e., Figures 35 and 37).

The intensity of bands in Figure 36 of the original submission was much lower than those in Figures 35 and 37 of the same document. This is quite apparent upon comparison of the 1.4 kb band intensity from each figure. The absence of the endogenous bands in Figure 36 was likely a result of loading less DNA on that gel or poor transfer efficiency. Despite the technical difference, the banding patterns present in each figure are internally consistent and support stability of the insert within the F10 genome. The data presented in Figure 37 are sufficient to show genomic stability from G0 through G3 as the important comparison is between DNA isolated from the starting and final generations.

ii. In the Southern blot of G0 and G2 wt and J3 DNA probed with AGP (i.e., Figure 50), the endogenous 5.0 kb band was absent despite the fact that this band was observed on Southern blots of G0, G1, and G3 wt and J3 DNA samples (i.e., Figures 49 and 51).

Similar to the previous question, one blot, Figure 50, in this series appeared to include less DNA or have reduced transfer efficiency than the others. Once again, the pertinent comparison is presented in Figure 51, which shows all expected bands and allows comparison of G0 to G3 in both J3 and J55.

g. In the table summarizing potato event F10 fragments which hybridized with the DNA probes (i.e., Table 7), it is indicated that a single 7.2 kb F10-specific fragment is present but in the corresponding Southern blot (i.e. Figure 12), two F10-specific fragments are observed. Please comment on this discrepancy.

In our original analysis, the second band was not interpreted to be specific to F10, but was inadvertently labeled as such in Figure 12. Due to weak hybridization and inconsistencies when using the A/T-rich PHL probe, we have transitioned to another probe specific to the adjacent R1 sequence. To remove any question, we repeated the Southern blot in question and hybridized with the PHL and R1 probes, independently (Figure 4). A single F10-specific band of the same size was observed in both blots, which is consistent with our proposed structure and data interpretation (Table 7) provided in the original submission.

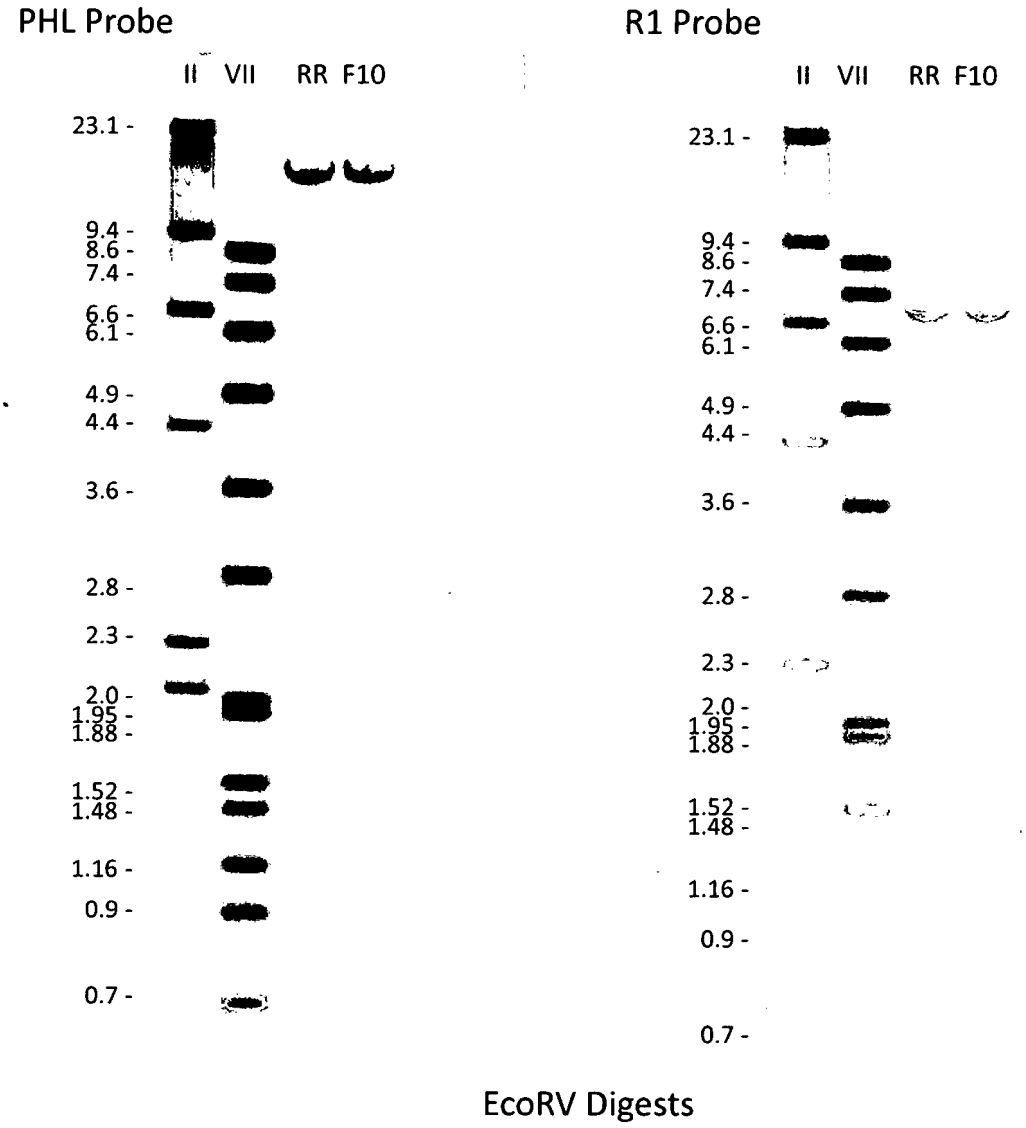


Figure 4. Southern blots of EcoRV-digested DNA hybridized with either a PHL (left) or R1 (right) probe. Ranger Russet (RR) and Ranger Russet F10 (F10); left two lanes are molecular weight markers, DIGII (II) and DIGVII (VII), respectively.

h. In the Southern blot of EcoRV-digested potato event F10 DNA probed with the AGP probe (i.e., Figure 10) , there appears to be a faint band around 9.4 kb which is not found in the control sample. Please comment on the presence of this band.

To verify our interpretation of the Southern blot in question (Figure 10 from original submission), we repeated the study. As shown in Figure 5 below, all high molecular weight bands were common to the F10 and WT samples. Thus, there are no bands unaccounted for in our Southern blots.

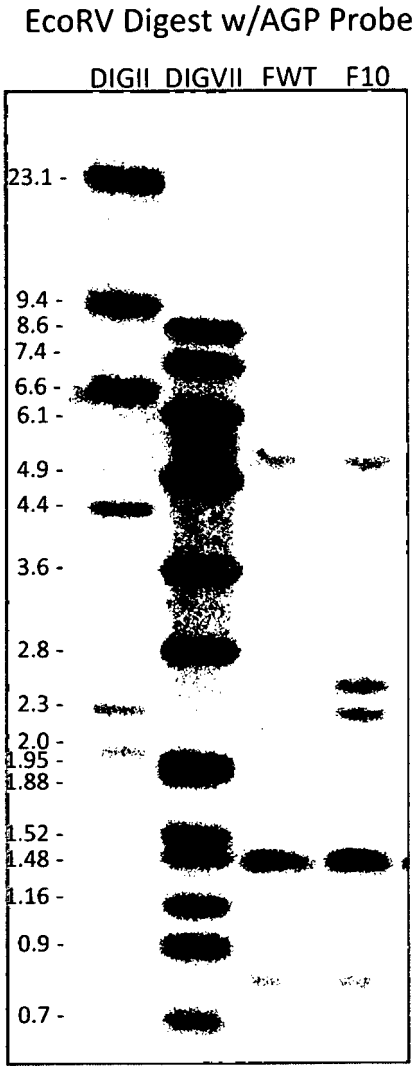
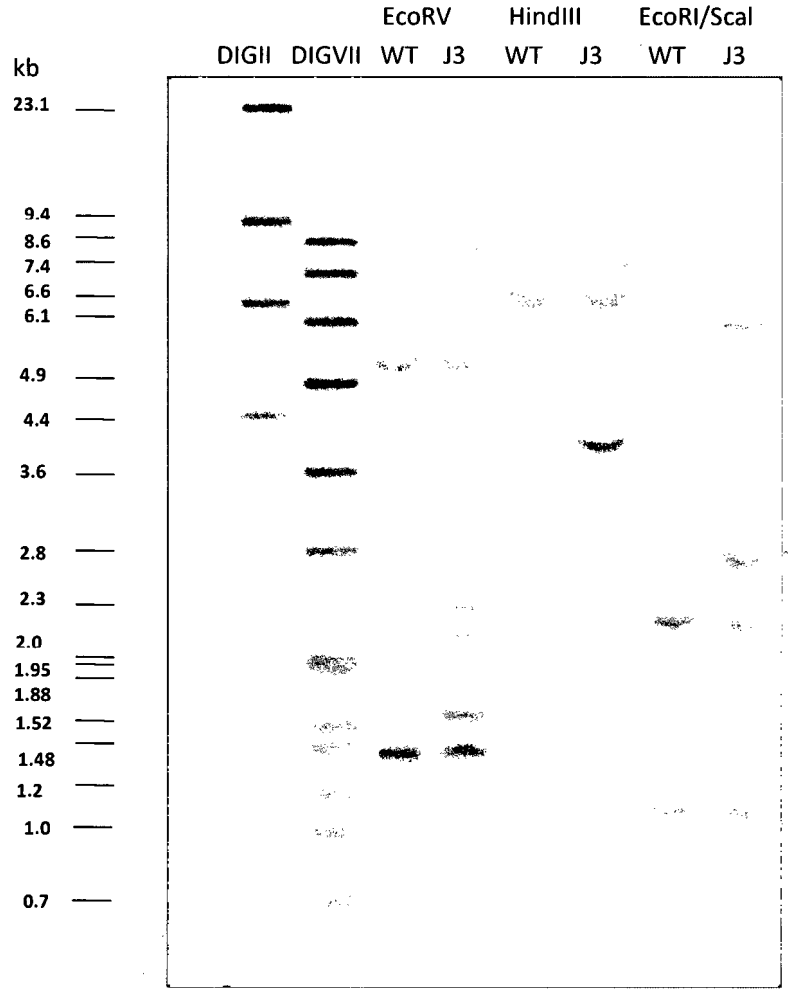


Figure 5. Southern blot of EcoRV-digested DNA hybridized with AGP probe. Ranger Russet (FWT) and Ranger Russet F10 (F10); left two lanes are molecular weight markers, DIGII and DIGVII, respectively.

i. In the Southern blot of EcoRI/ScaI-digested potato event J3 DNA probed with the AGP probe (i.e., Figure 20) , the 2.9kb band appears to be of double intensity. Please comment on the possible causes for this double intensity binding.

The double intensity of the 2.9kb band in the J3 sample of Figure 20 (original submission) is due to co-migration of two independent digestion products, one from the original host (i.e. endogenous) and another specific to J3. This phenomenon is more clearly represented in Figure 6 (below), which is a reproduction from ***Appendix A1 - Revised Genetic Characterization of Atlantic Event J3*** (labeled as Figure 5 therein). This appendix was submitted to CFIA Feeds, PBRA, and Health Canada on September 3, 2014.



EcoRV	HindIII	EcoRI / ScaI
OB 8.4	JB 7.4	
JB 7	OB 6.6 OB 6.1	IB 6.7**
OB 5.3		
	IB 4.2**	OB 3.8 IB 3.7
		JB 2.9 OB 2.9
IB 2.3 OB 2.1		OB 2.2
IB 1.6** OB 1.4		
		OB 1.1

Figure 6. Atlantic DNA Hybridization with the AGP Probe. Genomic DNA of Atlantic control (WT) and Event J3 were digested with EcoRV, HindIII, and EcoRI/ScaI and hybridized with the AGP probe. Size of the DigII and DigVII molecular weight markers are indicated adjacent to the blot image. The estimated sizes of bands are summarized

in the table and classified into three groups based on the structure of the DNA insert: original endogenous bands (**OBs,** in green), internal bands (**IBs**) and the junction bands (**JBs**). DNA fragments of the pSIM1278 insert are in red. * Indicates a higher intensity band represented by multiple bands of the same size. ** Indicates higher intensity band represented by multiple probe binding sites on a given band. All molecular weights are presented in kilobases (kb).

j. In the Southern blot of HindIII-digested potato event J3 DNA probed with the GBS probe (i.e., Figure 23) , the 12 kb band appears darker than other bands. Please comment on the possible causes for this increased intensity of binding.

Our follow up molecular studies of J3 led us to an altered structure for the insert that accounts for all the band intensities in question. Please refer to ***Appendix A1 - Revised Genetic Characterization of Atlantic Event J3***.

7. Potato event TT4 was used as positive control in Southern blots used to detect backbone sequences (i.e. Figures 27-29). This event was reported to possess most, or all, of the pSIM1278 vector but no data was provided to demonstrate that this was the case. Please provide additional information on the copy number and intactness of the DNA inserts present in potato event TT4 to support its use as a positive control.

The following image shows a representative Southern blot performed during line selection where a number of backbone-positive lines were identified. The plasmid control (p1278) is loaded as a copy number control representing the equivalent of a single DNA copy in the genome. The intensity of the plasmid control band was similar to the insert bands within lines testing positive for backbone DNA, including TT4. Thus, TT4 contains a single copy of the backbone. These analyses are standard practice in our line selection.

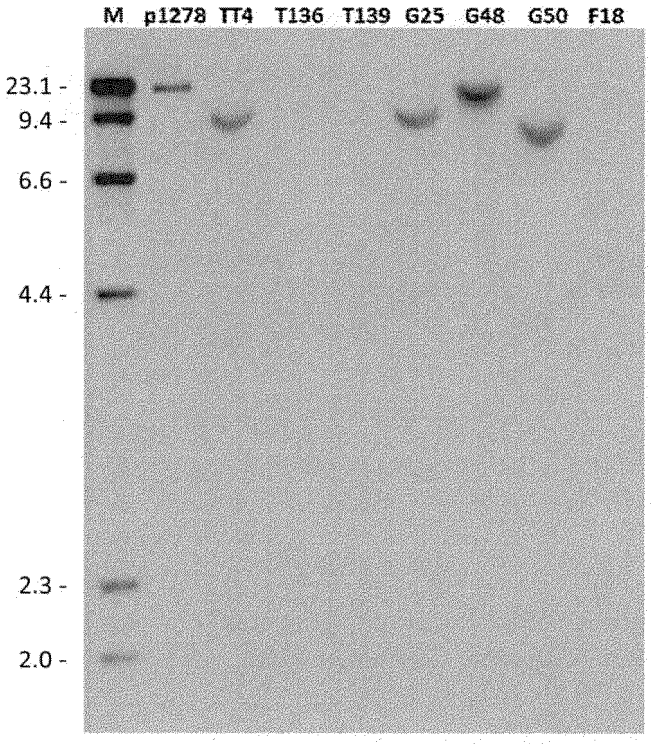


Figure 6. Southern blot of EcoRI-digested DNA from plasmid control (p1278) and seven events, including TT4. The blots were probed with backbone probe 1. DIGII Molecular weight ladder (M).

In our backbone DNA studies, we load the same amount of genomic DNA as in the studies evaluating the insert in each event. As we were able to detect a single copy of the insert in all of those studies, the sensitivity of our backbone-specific probes is confirmed. All backbone probes readily and robustly detected the backbone in TT4 control samples, including an endogenous band with probe 6, which hybridizes to a backbone region derived from the potato genome (i.e. Ubi7 promoter). Combined, our data strongly suggest that TT4 consists as a single insert and with a single copy of each element in the genome of TT4. The bands detected by probes 2-5, which recognize internal bands, were of the expected restriction fragment sizes for an intact backbone, and did not include any anomalous bands expected by duplication events. A single junction band was detected by probes 1 and 6, indicating a single insertion site in the genome. Introduction of multiple copies of the backbone at a single locus would result in additional bands not detected in our analysis, whereas multiple inserts would lead to unaccounted-for junction bands. As neither of these was true, the data strongly support the presence of an intact, or nearly intact, single copy of the pSIM1278 backbone in TT4.

The presence of the *ipt* cassette in the backbone results in developmental phenotypes, which is part of our marker-free transformation selection (Chapter 2 of original submission). As a result, it is difficult to maintain these plants for multiple generations, but even harder when multiple copies of backbone exist.

8. **To further demonstrate that backbone sequences were absent from potato events E12, F10, J3, and J55, PCR was used to amplify fragments indicative of junctions between DNA insert border regions and flanking backbone DNA or regions within the backbone DNA that flank the DNA insert. It was not clear whether the PCR primers used in these assays were capable of detecting all backbone sequences or only those associated with the characterized insertions in potato events E12, F10, J3, and J55. Please elaborate further on the specificity of these primers.**

   The primers in question were not designed to be specific to the events, but instead were designed to detect the presence of the junctions between the backbone and T-DNA from pSIM1278, should they exist in the transformed events. These PCRs corroborated the Southern blot results and verified the absence of the backbone sequences with the highest probability of integration during transformation. The inability to detect these sequences strongly supports the Southern data and indicates the absence of backbone DNA in these events.

   As part of our characterization, we have determined the sequences of both junctions at the insertion site in the potato genome for each event. None of these junctions contain backbone DNA sequence, which conclusively shows the absence of backbone DNA at the most likely location in the genome – the site of the actual T-DNA insertion.

9. **Please comment on the potential that new open reading frames may have been created during DNA insertion in potato events E12, F10, J3, and J55 which would be expected to result in generation of newly expressed proteins (e.g. whether they are associated with regulatory sequences that are expected to be functional in the potato events).**

   A complete bioinformatics assessment of the allergenicity, toxicity, and open reading frames of each insert is included as **Supplement E: Bioinformatics Analysis of Inserts**. We did not identify any safety concerns for any of the events under consideration.

10. **In the section describing Stability of Inserted DNA (i.e. Section 5) it is referenced that the G1 generation was the "first generation of field grown plant (after tissue culture)". In section 5.1 Methods and Materials for Determining Insert Stability it states "For generation-1 (G1) analysis, two propagated plants from each event and one plant from each control were planted in the greenhouse; one of the tubers harvested from each plant was planted to obtain leaves from the G1 plants that were used to isolate DNA and evaluate the F1 generation". Please confirm if the G1 generation was field grown or greenhouse grown.**

    The text in chapter 5 should have indicated that G1 material was greenhouse grown:

    "G1 First generation greenhouse grown plant (after tissue culture)"

11. In section 5.1 Methods and Materials for Determining Insert Stability, the text describing DNA Isolation only references leaf tissue. In the G3 generation genomic DNA was extracted from tubers. Please describe the DNA isolation method for tuber tissue.

The DNA extraction method was the same (i.e. CTAB method described in section 5.1) regardless of tissue type. Tuber tissue was lyophilized prior to grinding and extraction.

12. In section 5.1 Methods and Materials for Determining Insert Stability, the text indicates that all G0, G1, and G2 DNA was obtained from leaves and G3 DNA was obtained from tubers. Please explain why G3 DNA was isolated from tuber tissue and not from leaf tissue like the other generations.

The transition from leaf to tuber DNA was based upon a better fit with our field harvest protocol. For G3 material it is more convenient to isolate DNA from the tubers isolated at crop harvest than make a separate trip to the field simply to get the leaf material. The two tissues are genetically equivalent.

13. Please indicate the generation(s) used for the molecular characterization studies.

The material used for the molecular characterization was derived from the leaves of G1 material grown in the greenhouse and subsequently confirmed for genetic stability using FG2 and FG3 as described in Section 5.1 of the original submission.

CFIA Only Questions:

1. **The CFIA requires that a method of detection and identification be provided for plants with novel traits and novel feeds from plant sources. The criteria for such methods are available on the CFIA website; http://www.inspection.gc.ca/plants/plants-with-novel-traits/applicants/detection-and-identification/eng/1338224521085/1338229770701. The method provided with the submission was reviewed and the following criteria were not addressed.**

   a. **Agreement to provide appropriate reference materials to the CFIA upon request was not provided.**

      J.R. Simplot agrees to provide the appropriate reference materials upon request.

   b. **Contact information for a technical support person was not provided.**

      Simplot Plant Sciences

      5369 W. Irving Street

      Boise, ID 83706

2. **Please confirm that the expected livestock feed usage of potato events E12, F10, J3, and J55 would not be altered, compared to conventional potatoes.**
   That is true.

In addition to these questions, we have the following comments for your consideration. A response to these comments is not mandatory for the molecular assessments of your submission but may be supportive.

1. **No information was provided on how the levels of the new traits incorporated into potato events E12, F10, J3, and J55 (i.e. polyphenol oxidase levels, reducing sugar levels, asparagine levels) compare to the ranges of levels of these traits present in potatoes currently grown and utilized in Canada. While it is not mandatory to provide this information for a new trait, if the levels of a new traits are similar to or within the range of these traits currently found in potatoes, this information is supportive of safety.**

2. **According to the legends accompanying the Southern blots used to establish the structure and copy number of potato event E12, F10, J3, and J55 (i.e. Figures 10-13, 15-18, 20-23, and 25), original (endogenous) bands are presented by a closed black triangle, internal bands are represented by an open grey triangle, and junction bands are represented by a closed grey triangle. In the Figures, however, internal bands are also identified by an open black triangle and for some of the grey arrows, it was not clear if they were open or closed (e.g. the 2.6 kb JB observed on the EcoRV digest of potato event F10 DNA probed with the AGP probe – Figure 10). Please adopt a more consistent labeling approach for future submissions.**

   Thank you for the feedback. We have made changes to our labeling and data presentation to improve readability, which have been incorporated into the previously submitted document, ***Appendix A1 - Revised Genetic Characterization of Atlantic Event J3***. Any additional feedback after review of that document would also be appreciated.

The review of this submission will continue once the above information is received. If you have any questions please feel free to contact us.

Supplement A: Molecular Pathways and Characterization

The pSIM1278 insert contains two native promoters (pGbss and pAgp) that promote transcription of inverted repeats, primarily in the tuber, containing small fragments of DNA from four different genes (Asn1, Ppo5, R1, and Phl), which results in silencing of those same target genes using RNA interference. References to the origins of all sequences in the pSIM1278 construct including Genbank accession numbers that include further references were provided in Table 4 of the original submission. The isolation, cloning, and characterization of the gene fragments were performed by scientists at the J.R. Simplot Company. (Rommens et al., 2006).

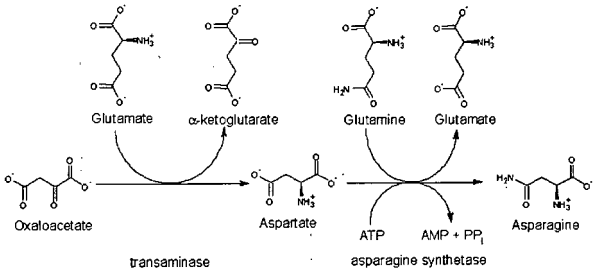
The introduced DNA does not code for any proteins and thus there are no potential allergens or toxins introduced into the potato. Furthermore, there is no evidence that any of the four genes targeted are known toxins, allergens, pathogenicity factors, or irritants, but if they were the gene silencing technology would reduce their expression, not increase it. A full bioinformatics characterization of potential allergens and toxins arising from the insert is provided in ***Supplement E: Bioinformatics Analysis of Inserts***.

The genes were chosen for targeting based upon their biochemical roles in asparagine production, accumulation of reducing sugars, or black spot bruising. The rationale, strategy, and mode of action for each protein were previously described and are summarized below (Chawla et al., 2012; Rommens et al., 2006, 2007, 2008).

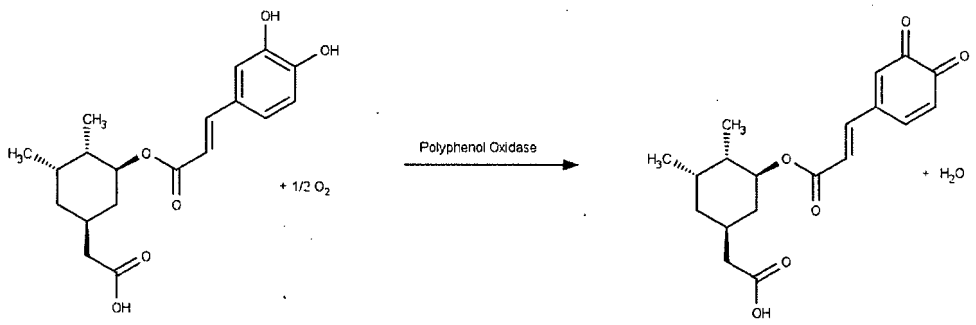
ASN1 (Asparagine Synthetase 1) ASN1 catalyzes the conversion of glutamine to asparagine by transferring the side-chain amine (NH_2) from glutamine to aspartate to form asparagine. Glutamine and asparagine are critical amino acids for plant growth and development because of their role in nitrogen utilization and transport. Lack of photosynthetic activity results in a higher N:C ratio signaling increased *Asn1* transcription. Higher ASN1 protein levels in dark-adapted plants lead to the accumulation of asparagine (McGrath and Coruzzi, 1991).

Asparagine is a substrate of the Maillard reaction which converts amino acids and reducing sugars to acrylamide during high-temperature processing. Unlike asparagine, glutamine does not contribute to the formation of acrylamide (Mottram et al., 2002). Reduction of ASN1 and asparagine levels in potato tubers by Innate™ technology results in decreased levels of acrylamide in cooked potato food products.

Ppo5 (Polyphenol Oxidase 5) Polyphenol oxidase catalyzes the conversion of *o*-diphenols to *o*-



quinones. The reactive *o*-quinone auto-polymerizes to form melanins, which are responsible for the coloration of oxidized plant tissues. The biological significance of these phenolic conversions is unknown (Mayer, 2006). An example of the activity of polyphenol oxidase is the conversion of the natural substrate, chlorogenic acid, to a quinone:



Starch-related R1 Protein (α-glucan, water dikinase) R1 catalyzes the transfer of the γ- and β-phosphates of ATP (through a phospho-histidine intermediate) to α-glucan and water, resulting in phosphorylated starch. R1 is mainly responsible for phosphorylation at the C6 position. Phosphorylation affects the degree of crystalline packing within the starch granule and makes it more accessible to degradation. Thus, loss of R1 activity impairs starch degradation, which reduces accumulation of reducing sugars (Ritte et al., 2002, 2006).

$$\alpha\text{-glucan} + ATP + H_2O \rightarrow \alpha\text{-glucan-P} + AMP + P_i$$

PhL (α-glucan phosphorylase, starch phosphorylase L) Phosphorylase L degrades starch by phosphorolytic release of glucose-1-phosphate from glucan chains. Gene silencing in potato and mutation in *Arabidopsis* do not alter total starch levels, but a loss of the enzymatic activity will limit reducing sugar accumulation (Sonnewald et al., 1995; Zeeman et al., 2010).

$$\alpha\text{-glucan(n)} + P_i \rightarrow \alpha\text{-glucan(n-1)} + \text{glucose-1-phosphate}$$

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Supplement B: Analysis of pSIM1278 siRNA Targets and Specificity

Cellular gene expression is tightly regulated in cells at both the transcriptional and post-transcriptional levels. RNA interference (RNAi) is one of nature's post-transcriptional regulatory pathways used to limit expression of a particular gene. The mechanism is initiated by a double-stranded RNA (dsRNA) precursor that contains sequence corresponding to a target messenger RNA (mRNA) in the cell. In general, half of the dsRNA molecule matches a target gene and the other half consists of complementary sequence. A cellular RNase III enzyme, Dicer, recognizes and processes the longer dsRNA molecule into small 21 bp duplexes consisting of two individual strands termed siRNA (Figure 1A). These siRNA duplexes are subsequently bound by the RNA Induced Silencing Complex (RISC), which selectively degrades one of the two strands, referred to as the passenger strand (Figure 1B, red). The remaining strand, referred to as the guide strand (Figure 1B, blue), serves to activate RISC and turn it into a silencing complex. The activated RISC destroys those mRNA that it contacts, in which the retained siRNA has complete complementarity with the mRNA (Figure 1B).

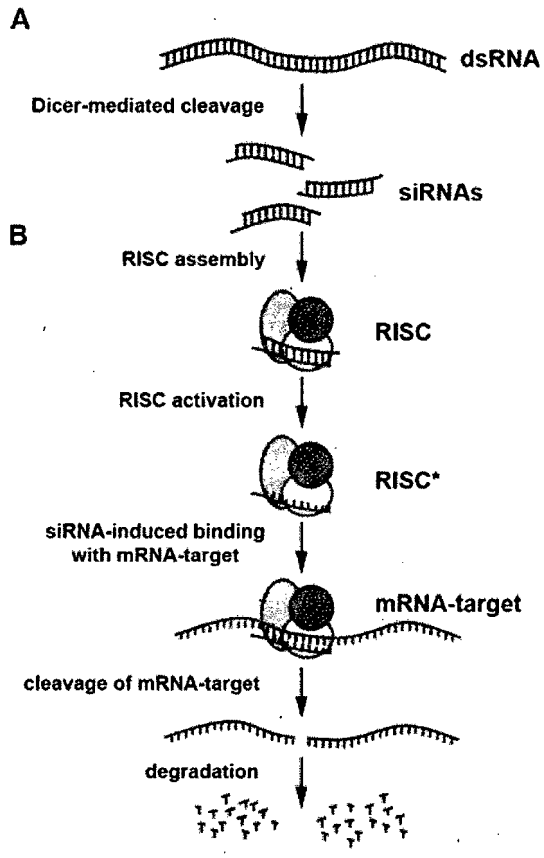

Figure 2 Schematic of RNAi (Petrova et al., 2013).

The cleavage of these target RNAs can lead to reduced expression of the associated protein, but silencing efficiencies can vary dramatically for individual siRNA (Petrova, Zenkova, & Chernolovskaya, 2012). Some organisms, including plants, possess a related process where an RNA-Dependent RNA Polymerase (RdRP) uses the cleaved mRNA as a template to generate additional siRNAs (22 nts) referred to as secondary (2°) siRNA, which also have the potential to silence the target message.

Although a single siRNA is sufficient to direct cleavage of an mRNA, not all siRNAs are equally effective at cleaving mRNA. For this reason, it has become common when working with plants to design inverted repeats with stem regions containing 100-1000 base pairs (bp) to serve as silencing triggers (Hirai & Kodama, 2008). The transcription product of the inverted repeat is an intramolecular double-stranded RNA structure that is processed by Dicer into siRNA duplexes as described in Figure B.1.

The use of bioinformatics assessments to identify off-target effects in plant biotechnology has been controversial due to limitations and challenges associated with data interpretation. There are numerous limitations to these approaches, most of which lead to over representation of the number of off-targets. Based upon many experimental observations, we know that not all of the siRNAs in cells are stable and effective at inducing silencing and that identity between

siRNAs and sequences in a database does not necessarily predict productive interactions. Nonetheless, in this study we have performed an exhaustive analysis of all potential siRNA that could arise as a result of processing the pSIM1278 inverted repeats with the mRNA targets contained in the Michigan State University (MSU) transcript reference database for potatoes (Sharma et al., 2013). The predicted off-target RNAs identified should be considered with the following caveats in mind:

1. As mentioned earlier and shown in Figure 1B, each siRNA duplex consists of a guide strand and a passenger strand. The passenger strands do not have silencing potential as they are selectively degraded prior to RISC activation. Thus, only half of the siRNAs that can be computationally predicted fall into the class of guide strands with the potential to direct mRNA target destruction. Bioinformatics approaches, such as the one described in this report, do not distinguish between guide and passenger strands, which means that the predicted target binding sites significantly over-represent the actual binding sites due to inclusion of passenger siRNA:mRNA interactions. As a result, the number of target interactions described is two-fold higher than might be observed empirically.

2. Expression of Innate™ siRNA are limited to tubers and don't appear to spread significantly within the plant. Thus, a target RNA must be expressed in the tuber with the siRNA for it to be silenced by the siRNAs generated from our inverted repeats, once again indicating that the siRNA off-targets identified in our analysis likely over-represent the number of real off-targets.

3. Although complementarity between siRNAs and potential targets is important for specificity, it is generally appreciated that there are contextual effects of nearby sequence on the target RNA. That is, sequences distinct from the siRNA binding site on the target RNA can prohibit or promote target silencing (Liu, Li, Lin, & Zuo, 2013; Luo & Chang, 2004; Overhoff et al., 2005). The local effects are complicated and not fully understood, which makes it challenging to identify which RNAs with complementarity are legitimate off-targets. It is possible the number of targets predicted by bioinformatics will over-represent the actual number of off-targets.

4. The relative abundance of siRNAs and all potential targets will also influence silencing potential. RNAs that are low in abundance are less likely to be silenced in the presence of the abundant targets based upon binding kinetics – again leading to over-representation of siRNA targets.

5. Mechanisms such as compensatory transcriptional activation have highlighted ways in which plants can overcome attempts to silence important RNAs in the plant. Since many genes are tightly regulated by feedback mechanisms, it is not surprising that

transcriptional activation would be up-regulated in an attempt to overcome unwanted silencing of particular RNAs in the cell. The AP2 gene provides an excellent example where it compensates for undesired miRNA silencing through increased transcription to ensure sufficient AP2 protein exists within the cell (Schwab et al., 2005).

6. It is unclear how broadly susceptible insects are to off-target effects related to ingesting siRNA through their diet. It is clearly not ubiquitous as organisms of the same genus (e.g. *Caenorhabditis elegans* vs. *Caenorhabditis briggsae*) are known to have differing susceptibilities (Nuez and Félix, 2012). Thus, even when transcriptome data is available to identify possible off-target effects in these organisms, it does not indicate the organism is susceptible to the siRNAs, nor does it provide any evidence they are consumed in sufficient quantities to produce physiological effects in susceptible organisms.

Due to the many challenges associated with predicting and analyzing siRNA off-targets, many regulatory bodies have questioned the value in performing such bioinformatics analyses. During a recent European Food Safety Authority meeting on RNAi-related food safety issues, these topics were discussed in great detail with contributions from academic, regulatory, and biotech industry participants (EFSA 2014). The consensus on this topic was that one should be cautious when considering the off-target effects of a bioinformatics analysis. Instead, bioinformatics results are best used to guide the design of inverted repeat sequences. Nevertheless, we include in this report a comprehensive analysis of off-target effects based upon the most robust potato transcript databases available at MSU.

Bioinformatics-based off target prediction

Our bioinformatics method for analyzing potential off-target effects in the potato was based upon a three-step process:

1. Identify all possible siRNAs that could be derived from the dsRNA structures associated with the inverted repeats in Innate™ potatoes.

2. Identify all known potato transcripts that have complementary binding sites for any of the siRNAs.

3. The gene description for identified transcripts was determined by cross-reference with a GFF-formatted database.

In plants, dsRNA can be processed into either 21-nt or 24-nt siRNA with production of 22-nt siRNAs generated through an independent mechanism. We focused our bioinformatics analysis on the most comprehensive class, 21-nt siRNA, as this will identify the most potential off-targets, including those that would be identified through analysis of 22-nt and 24-nt siRNA.

Table 1. Potential siRNA off targets for pR1/pPhL inverted repeat identified by bioinformatics.

Transcripts	Gene Identifier / Descriptor	Sequence identity (bp)[1]	Matching siRNA[2]
PGSC0003DMT400084175	hypothetical gene of unknown function	163	143
PGSC0003DMT400007913 PGSC0003DMT400007914	Tetraspanin10	64	44
PGSC0003DMT400026560	Leucine aminopeptidase, chloroplastic	33	13
PGSC0003DMT400045411	transport protein	28	8
PGSC0003DMT400071567	Hypothetical gene of unknown function	27	7
PGSC0003DMT400056074	UDP-glucuronosyltransferase	27	7
PGSC0003DMT400030708	AG-motif binding protein-3	26	6
PGSC0003DMT400027382	Homology to unknown gene	25	5
PGSC0003DMT400076925	Oxidoreductase / transition metal ion binding protein	25	5
PGSC0003DMT400000825	Hypothetical gene of unknown function	24	4
PGSC0003DMT400048985	Hypothetical gene of unknown function	24	4
PGSC0003DMT400069580	kinase interacting protein	23	3
PGSC0003DMT400043095	Pentatricopeptide repeat-containing protein, mitochondrial	23	3
PGSC0003DMT400009611	Bel1 homeotic protein	22	2

1. Sequence identity refers to the size of the contiguous region of complementarity between the transcript and the inverted repeat (e.g. number of independent siRNA + 20).

2. Matching siRNA refers to the number of independent siRNA predicted from the inverted repeats with complementarity to the particular transcript. All listed transcripts are associated with siRNA from the pPhL/pR1 inverted repeat. None were identified for the Asn1/Ppo5 inverted repeat.

The only targets identified for the Asn1/Ppo5 inverted repeat were the *Asn1* and *Ppo5* genes, which were targeted by design. Analysis of the pR1/pPhL inverted repeat identified 14 different genes that possessed complementarity to the potential 21-nt siRNA. The region of sequence identity between the inverted repeat and most of the identified transcripts was small compared with the hypothetical gene of unknown function and member of the tetraspanin family (Table 1).

There is no evidence of a phenotype or biochemical pathway that could be disrupted by the hypothetical gene, nor is there evidence that it serves as the source of a protein in the potato. The second gene belongs to the tetraspanin family of transmembrane proteins which are associated exclusively with eukaryotes and often duplicated in the genome. Arabidopsis contains 17 tetraspanin genes where only one, EKEKO, has been phenotypically characterized and was shown to function in leaf and root patterning during development (Wang, Vandepoele, & Van Lijsebettens, 2012). We have not observed any developmental phenotypes in our Innate™ potatoes that suggest tetraspanin10 is being silenced. If it is, the level of silencing is insufficient to produce a measurable phenotype in the host plant.

The rest of the identified targets have very limited sequence identity and are less likely to be actual off-target genes. None of them have clear biological roles that would allow us to evaluate functional silencing. Unlike our targeted phenotypes where we can measure downstream effects to know any measured silencing is biologically significant, we cannot do the same for these genes.

Conclusion

We have performed a bioinformatics analysis to identify potential transcripts that could be inadvertently silenced through off-target effects in the potato genome. The Asn1/Ppo5 inverted repeat was shown to be highly specific as we did not detect any off-targets associated with the 21nt siRNAs; whereas a small number of transcripts may be off-targets of siRNA derived from the pR1/pPhL inverted repeat. However, none of the potentially-affected genes were known to, or expected to, have biologically critical roles in the potato or measurable phenotypes. Most importantly, none of the genes identified raised any concerns regarding safety.

Experiments designed to study the effects of overexpressing miRNAs in plants have identified plants with developmental defects, such as the absence of petals, sepal transformation into carpels, uneven leaf shape, delayed flowering time, and male sterility (Achard et al., 2004; Aukerman and Sakai, 2003; Chen, 2004; Palatnik et al., 2003; Schwab et al., 2005). Agronomic line selection of Innate™ potatoes ensures only lines with normal morphological and developmental profiles are propagated to prevent phenotypes associated with off-target effects.

In summary, a bioinformatics assessment of the inverted repeats contained in the pSIM1278 plasmid used in the transformation of the Innate™ potatoes did not uncover a significant number of potential off-targets, and none of those identified were associated with pathways that suggested the potential for a safety concern. These conclusions are consistent with normal development, agronomic, and disease phenotypes of Innate™ potatoes in the field, as well as, compositional equivalence of tubers.

An analysis of potential off-target effects in organisms associated with the potato ecosystem was not possible due to limitations in transcriptome sequences. Since the siRNAs are only expressed in tubers, which are located below ground the potential for off-target effects is quite low and limited to a very small number of organisms. Our silencing constructs were not designed to target the open reading frames and therefore less likely to target sequences conserved between organisms, which further reduces the likelihood of an unexpected effect in another organism.

Methods

A Python script was used to identify all 21-nt siRNAs that could potentially arise from processing a particular inverted repeat (ASN/PPO vs. pPhL/pR1), which were deposited into FASTA-formatted files (siRNA_21mers_asn_ppo_stem.txt and siRNA_21mers_phl_r1_stem.txt). The siRNAs were compared to the current potato transcript database (56,218 sequences) available from the Michigan State University repository to identity perfect complementarity between siRNA and transcripts. An example of the search query is provided, where siRNAs is the FASTA database and pot31RNA is the transcript database:

blastn –task blastn-short –query siRNAs –db pot31RNA –out outfile.txt –outfmt 7 –perc_identity 100 –word_size 21 –strand minus

The search results were accumulated in text files and imported into MS Excel™ for evaluation. The file, "siRNA_offtargets_pSIM1278.xlsx", consists of a tab associated with each inverted repeat and the associated off-targets (expected targets removed for clarity). The last column (column M) in each data sheet was added manually by cross-referencing the subject identifier (column B) with the annotated potato database (e.g. Sequence ID Search) available from MSU (http://potato.plantbiology.msu.edu/integrated_searches.shtml) to determine the actual gene name.

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Supplement C: Safety Considerations for Nucleic Acid, including Double-Stranded RNA and siRNA

Safety of Nucleic Acids

In 2001, EPA established an exemption from the requirement for a tolerance for residues of nucleic acids that are part of a PIP (40 C.F.R. 174.507) under the Federal Food, Drug, and Cosmetic Act (FFDCA), noting that "[n]ucleic acids are ubiquitous in all forms of life, have always been present in human and domestic animal food and are not known to cause any adverse health effects when consumed as part of food" (66 Fed. Reg. 37817, July 19, 2001). FDA reached a similar conclusion, stating that nucleic acids were "generally recognized as safe" for purposes of FFDCA (57 Fed Reg. 22984, 22990, May 29, 1992).

Safety of Gene Silencing Methods

Crops, including tomato, squash, soybean, papaya, potato, and plum, with traits that resulted from RNAi, have been deregulated by APHIS and CFIA and evaluated for food safety by Health Canada and the FDA. In many of these products, a small piece of RNA interferes with production of an enzyme, and thus influences a quality or nutritional trait. Innate™ potatoes contain gene silencing cassettes for *Asn1, Ppo5, R1,* and *PhL*, all of which result in small RNAs that regulate gene expression. Such small RNA (sRNA), including siRNA, miRNA, and piRNA, in plants and animals are generally involved in regulating endogenous gene expression, repressing transposons, or targeting invading pathogens for destruction. The sRNA are ubiquitous in nature, including prokaryotes where sRNA have also been associated with the antiviral CRISPR pathway (Karginov and Hannon 2010). All of these pathways rely upon an RNase III endonuclease to process a double-stranded RNA (dsRNA) precursor into small effector RNAs that can be used to target RNA or DNA for modification or destruction. Due to bacterial colonization of our intestines and our daily diets of plants, animals, and fungi expressing their own spectra of sRNA, we are constantly exposed to a multitude of sRNA.

A publication by Chen-Yu Zhang's team claimed that a plant-derived miRNA had the potential to survive substantial obstacles to elicit a biological activity in the liver of humans and mice (L. Zhang et al. 2012). The implications of these findings led to a number of studies aimed at reproducing the author's study. However, these claims have not been substantiated (Dickinson et al. 2013; Snow et al. 2013; Witwer et al. 2013; Y. Zhang et al. 2012), and have been challenged by many experts in the field leading to self-correction of the scientific literature through publication of these numerous failed replication studies (Editorial 2013). The work of Dickinson and colleagues showed the physiological effects observed by Zhang et al. were actually a result of an unbalanced diet, rather than miRNAs (Dickinson et al., 2013).

The results of the Zhang manuscript were central to the argument put forth by Jack Heinemann and colleagues in a communication calling for more rigorous safety testing of RNAi-based biotech products due to potential off-target effects of sRNA (Heinemann et al. 2013). The concerns of Heinemann and colleagues were thoughtfully considered by fellow scientists associated with the bi-national governmental regulatory agency, Food Standards Australia New Zealand (FSANZ), which evaluates food safety requirements for biotech foods. In their formal

response, FSANZ concluded, "The weight of scientific evidence published to date does not support the view that small dsRNA in foods are likely to have adverse consequences for humans" (FSANZ 2013).

The history of safe use, complexity of the human GI tract, irreproducibility of the cited controversial manuscript (L. Zhang et al. 2012), our compositional and nutritional data, and the unique characteristics of Innate™ potatoes collectively establish these potatoes as safe for human consumption. In fact, there is no scientific rationale to suggest that sRNA present in GM-foods are any less safe than those naturally abundant and safely consumed in our current diets.

Stability through Microvesicles or Protein Complexes. Another possible mechanism to increase stability of siRNA would be for the plant to package them into microvesicles (exosomes) or apoptotic bodies or bind them to large protein or lipid-protein complexes. Plants are not thought to package cellular material into apoptotic bodies or microvesicles for destruction by other cells, as is done in animals. Instead, during programmed cell death, they concomitantly shrink their protoplasm while destroying cellular contents in an effort to contain a pathogen within the original cell structure to maintain structural integrity (van Doorn et al. 2011). A large amount of programmed cell death would thus be associated with sick plants that are not included in the food production process. A recent highly-quantitative study found that there was far less than one miRNA per exosome in human samples, indicating that individual exosomes do not carry biologically significant numbers of miRNAs (Chevillet et al., 2014) and thus question their significance when detected in human tissue by highly sensitive sequencing methods (Lukasik and Zielenkiewicz, 2014). Thus, even if small numbers of siRNA/miRNA were to survive the digestive tract they are unlikely to have biological significance.

The biological activity of sRNA is linked to association with RNA induced silencing (RISC) complexes. A number of distinct cellular pathways exist in plants and animals for processing sRNA and executing their biological activities, where each pathway includes protein complexes that bind to longer dsRNA, siRNA duplexes, or the sRNA species (Pumplin and Voinnet 2013). These protein complexes are considered critical for stabilizing sRNA as unincorporated sRNA (i.e. passenger strand) are more rapidly turned over. Turchinovich and colleagues found that the vast majority (>97%) of miRNAs identified in their culture media and plasma samples were not contained within vesicles, but were instead protected from degradation by a protein involved in the RISC complex, which will not be taken up by cells (Turchinovich et al. 2011).

In summary, there is evidence that siRNA may be protected by association with RISC complexes within and outside of cells. However, since protein transport across cell membranes is highly regulated, these complexes may protect sRNA from degradation and prevent their indiscriminate uptake by human cells. The challenges of packaging sRNA have been realized by the pharmaceutical industry, which has spent considerable time and effort attempting to develop techniques aimed at optimizing the stability, delivery, distribution, and pharmokinetics of sRNA for use as orally delivered therapeutics with limited success (Castanotto and Rossi 2009; Scaggiante et al. 2011). One of the groups that rebutted the work by the Zhang group, miRagen Therapeutics, could have benefitted from confirmation of those studies.

Uptake of sRNA in Animals. While genes in some simple organisms can be targeted through feeding upon organisms expressing double-stranded RNA (dsRNA), this is highly unlikely in

higher organisms, such as humans. Humans have complex GI tracts that present numerous obstacles to the uptake of dietary RNA, have many more cells to prevent non-specific accumulation, and lack components of the RNAi pathway (e.g. RNA-dependent RNA polymerases) that could amplify and sustain a non-specific response (Petrick et al. 2013). In addition to the plethora of sRNA consumed through a normal diet, humans possess trillions of microbes within their digestive tracts that can both absorb and secrete their own sRNA, which have also been detected in human plasma samples (Wang et al. 2012).

Bioactivity of plant-derived sRNA in mammalian cells. The Lam lab investigated plants as a delivery system for siRNAs that could target viruses in consumers (Zhou et al. 2004), whereas the Lee lab explored the potential of using plants as an economical factory for production of siRNA (Chau and Lee 2007). These conflicting datasets are the only mammalian studies we are aware of that address bioactivity of plant sRNA in mammalian cells, but a study was performed in the model organism, *Caenorhabditis elegans*, which is a highly-sensitive system for inducing and detecting RNA interference activity. Consistent with the results of Chau et al., they did not find biological activity of plant-derived siRNA (Boutla et al. 2002; Chau and Lee 2007). Interestingly, they were able to induce an RNAi-mediated phenotype when injecting longer dsRNA derived from plants. These results may suggest the structure of plant siRNA are inconsistent with animal systems or that exogenous siRNA are much less efficient at inducing a biological phenotype than dsRNA being processed by the cell's own machinery. It remains unclear whether the very modest phenotype reported by the Lam group is dependent upon RNAi as they were treating cells with impure samples, including longer dsRNA that may have activated a cellular immune response.

Processing of dsRNA from inverted repeats in plants can produce multiple classes of sRNA, including 21-22 nt and 24 nt species. The 24 nucleotide population is especially unlikely to have RNAi activity in animals as they are not involved in degradation of target transcripts even in plants (Fusaro et al. 2006).

Summary of RNAi safety. In summary, humans consist of cells, tissues, and organs that remain homeostatic in the presence of varying diets consisting of abundant sRNA. It is highly unlikely that a sufficient quantity of these sRNA would survive the GI tract and accumulate in a given human cell resulting in a short-term, let alone a long-term, biological effect. In addition, the human body possesses a number of immune regulatory pathways dedicated to specifically detecting and destroying exogenous dsRNA as a means of protecting against foreign invaders.

Scientific rationale of the safety of orally ingested siRNA(s) derived from Innate™ potatoes. As described previously, the scientific literature does not support a model whereby sRNA present in consumed food pose a safety risk to humans following consumption (Petrick et al. 2013). In contrast there is a long record of safe consumption of sRNA within our natural diet. There are a number of important characteristics of our Innate™ potatoes and their use of RNAi:

- The Innate™ potatoes rely upon potato genomic DNA to initiate gene silencing using the plant's endogenous pathway. The inverted repeat sequence is derived from the sequence of the genes that are already being expressed in the potato.

- Many common potato preparation or cooking practices involve heating at high temperatures, which result in the conversion of asparagine with sugar into acrylamide, which has been associated with health concerns (Health Canada 2013). Innate™ potatoes use RNAi to reduce the accumulation of the precursor asparagine to limit acrylamide potential. Thus, Innate™ potatoes provide a consumer product with potentially enhanced safety.

- Processing of potatoes by consumers or the food industry involves treatments that are likely to limit the amount of sRNA in the final product. In addition to high temperature heating, treatments such as blanching, frying, dehydration, and freezing are commonly used, which lead to degradation and fragmentation of double-stranded genomic DNA. A similar fate is expected for sRNA as was shown in processed milk (Chen et al. 2010).

- The Innate™ potatoes under consideration do not target an evolutionarily conserved exogenous animal gene as might be the case when RNAi is used as a plant incorporated protectant. Since RNAi in Innate™ potatoes exclusively target plant genes, they are less likely to have adverse off-target effects in animals.

- We have performed rigorous compositional, nutritional, and agronomic analyses and have not observed any evidence of off-target effects in the plant where expression of sRNA was the highest and the potential for off-target effects greatest.

Numerous physiological barriers have impeded introduction of nucleic acid through oral uptake (O'Neill et al. 2011), and as noted previously, there is a long history of safe use associated with eating foods containing sRNA due to its ubiquitous presence in nature (Ivashuta et al. 2009; Jensen et al. 2013; Petrick et al. 2013). Mechanistic studies of a number of cultivars have shown plants selected for agronomic traits using conventional breeding techniques are using RNAi to silence their own genes through expression of inverted repeats (Della Vedova et al. 2005; Kusaba et al. 2003; Tuteja et al. 2004).

Comments presented to the EPA's Scientific Advisory Panel Public Meeting on RNAi technology as a pesticide, held January 28, 2014, included support for the safety of dsRNA by experts in the field (Mello 2014). Dr. Mello reported that oral uptake of dsRNA has proven unfeasible as a drug delivery route, thus unlikely to cause off-target effects when used for gene silencing in plants. He also reported that ingested RNA is rapidly metabolized in the gut where it is converted to nutrients, thus proposing that bioinformatics testing for similar sequences in humans would be unnecessary. Also, RNA is digested rapidly, suggesting that digestibility assays would be unnecessary for dsRNA.

In summary, we believe the history of safe use, the irreproducibility of the cited controversial manuscript (L. Zhang et al.2012), the submitted compositional and nutritional data, and the unique characteristics of Innate™ potatoes collectively establish these potatoes as safe for human consumption.

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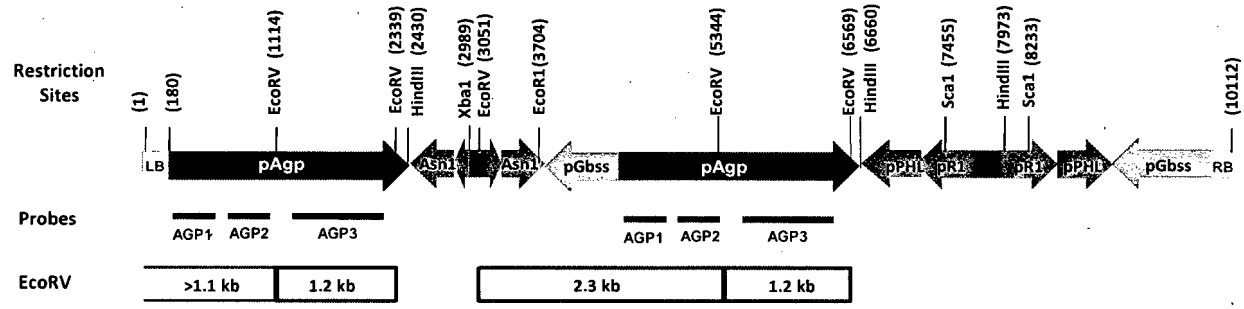
Supplement D: Supporting Southern blot studies using AGP2 and AGP3 probes

This document contains supporting Southern blots used to determine the structure and copy number of the E12, F10, J3, and J55 inserts. Due to the large size of the AGP promoter (>2kb) contained in the pSIM1278 insert, multiple probes are used to verify insert and copy number. As shown in Figure D.1, we have three probes (AGP1, AGP2, and AGP3) that hybridize to different regions of the AGP promoter. Two of the probes (AGP1 and AGP2) hybridize to the 5' half of the promoter upstream of the internal EcoRV site; whereas AGP3 hybridizes to the 3' end of the element (Figure D.1). In the absence of complex rearrangements or deletions, the same banding pattern is expected when EcoRV-digested genomic DNA is hybridized with AGP1 and AGP2, whereas a 1.2kb internal band is expected when probed with AGP3.

Figure D.1 Plasmid pSIM1278 and AGP probes



LB = Left Border like region containing 25-bp Left Border and 162-bp flanking sequence.
RB = Right Border like region containing 25-bp Right Border and 161-bp flanking sequence.

A Southern blot of EcoRV-digested genomic DNA from each event and the appropriate control probed with AGP2 is provided in Figure D.2A. As expected, these samples were equivalent to the same digests probed with AGP1 (compare to Figures 10, 15, and 20 in the original submission) and were consistent with the proposed structures (Figure D.3, A-D). In addition to the expected 2.3 kb internal bands and junction bands common to all events, J3 has an additional 1.6 kb internal band as indicated by its unique structure (Figure D.3C). One junction band was observed for E12 (2.2 kb), F10 (2.6 kb), and J3 (6.6 kb) confirming the presence of a single copy. The doublet indicating the presence of both a 2.2 and 2.3 kb band for E12 in Figure D.2A did not reproduce well in the figure, but is clearly distinguishable in the original blot (Figure 15). Consistent with the structure of J55 (Figure D.3D), J55 contains two junction bands (5.0 and 1.9 kb) and supports the presence of a single insert in this event as well.

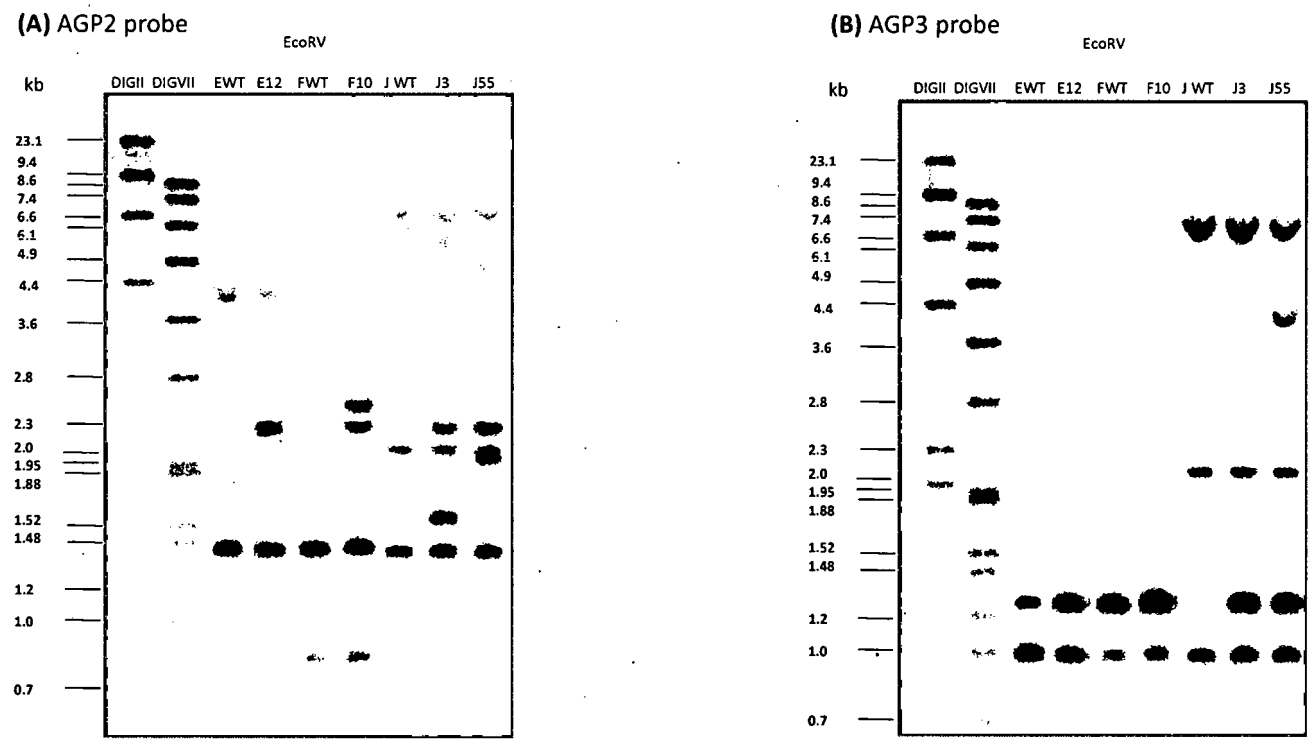
The AGP3 probe hybridizes to a region flanked by EcoRV sites and thus results in a 1225-bp (1.2 kb) band in all of the events (Figure D.1). This band comigrates with an endogenous species in the Russet Burbank and Ranger Russet samples, but clearly has higher intensity in the E12 and F10 samples. The only event to contain an additional AGP3 band is J55, which contains a truncated copy of Agp in its structure (Figure D.3D) resulting in the loss of a flanking EcoRV site and thus a larger 4.5 kb band (Figure D.2B).

The Southern blot of J55 digested with EcoRV and probed with AGP1 in the original submission contained an error as a marker indicated the presence of a high molecular weight band specific to J55. The validity of this band was unclear in the original blots and was not predicted by the

structure. Therefore, we repeated those experiments and provide more conclusive blots in Figure D.4 showing the high molecular weight species are common to both Atlantic and J55, which is consistent with a single insert and the proposed structure (Figure D.3D).

In conclusion, the Southern blot analyses with AGP2 and AGP3 probes supported the structures of pSIM1278 inserts in E12, F10, J3 and J55, which were presented in the petition.

Figure D.2. Southern blots hybridized with AGP2 and AGP3 probes



Genomic DNA was digested with EcoRV and hybridized with the (A) AGP2 or (B) AGP3 probe. EWT (Russet Burbank), E12 (Russet Burbank E12), FWT (Ranger Russet), F10 (Ranger Russet F10), JWT (Atlantic), J3 (Atlantic J3), and J55 (Atlantic J55). DigII and DigVII molecular weight markers are labeled adjacent to the blot in kilobase pairs (kb).

Figure D3. Structures of E12, F10, J3, and J55 inserts

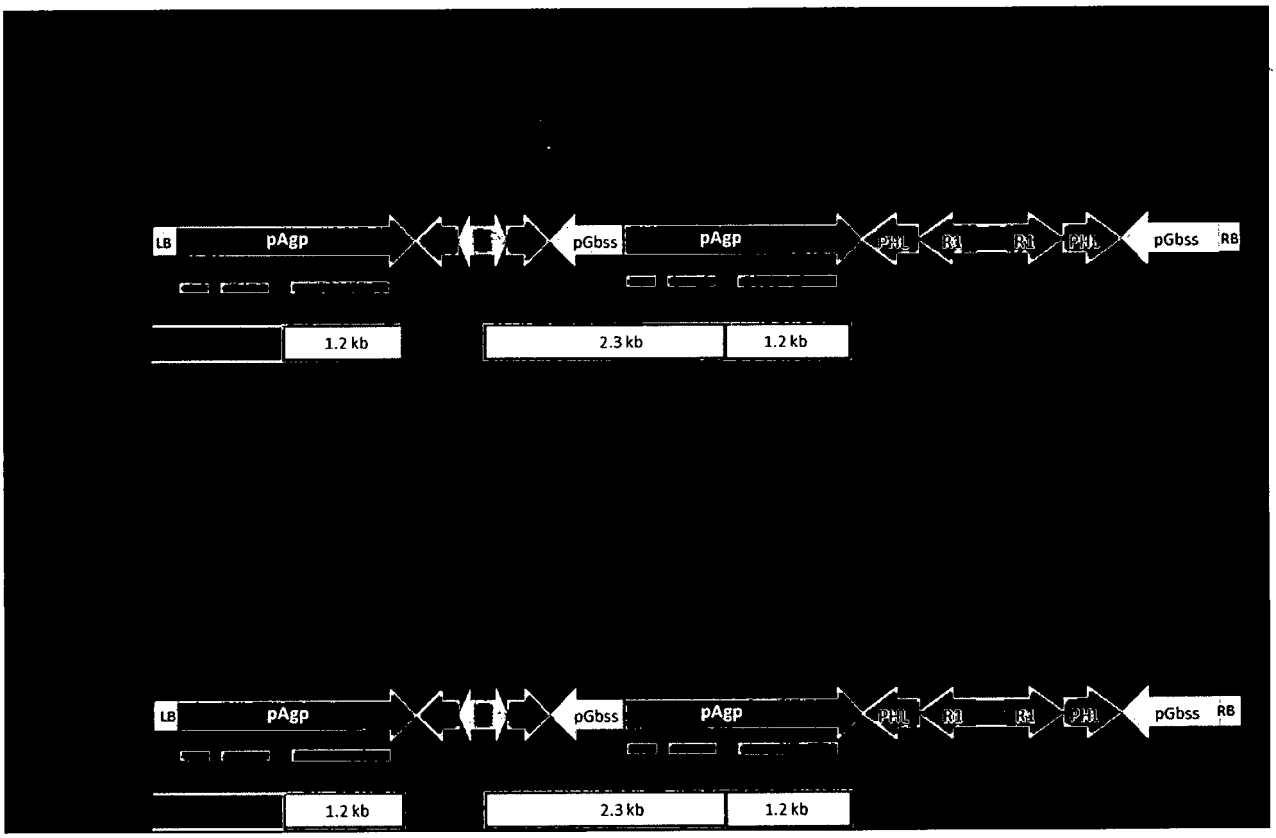


Figure D.3. Structures of E12, F10, J3, and J55 inserts (Continued)

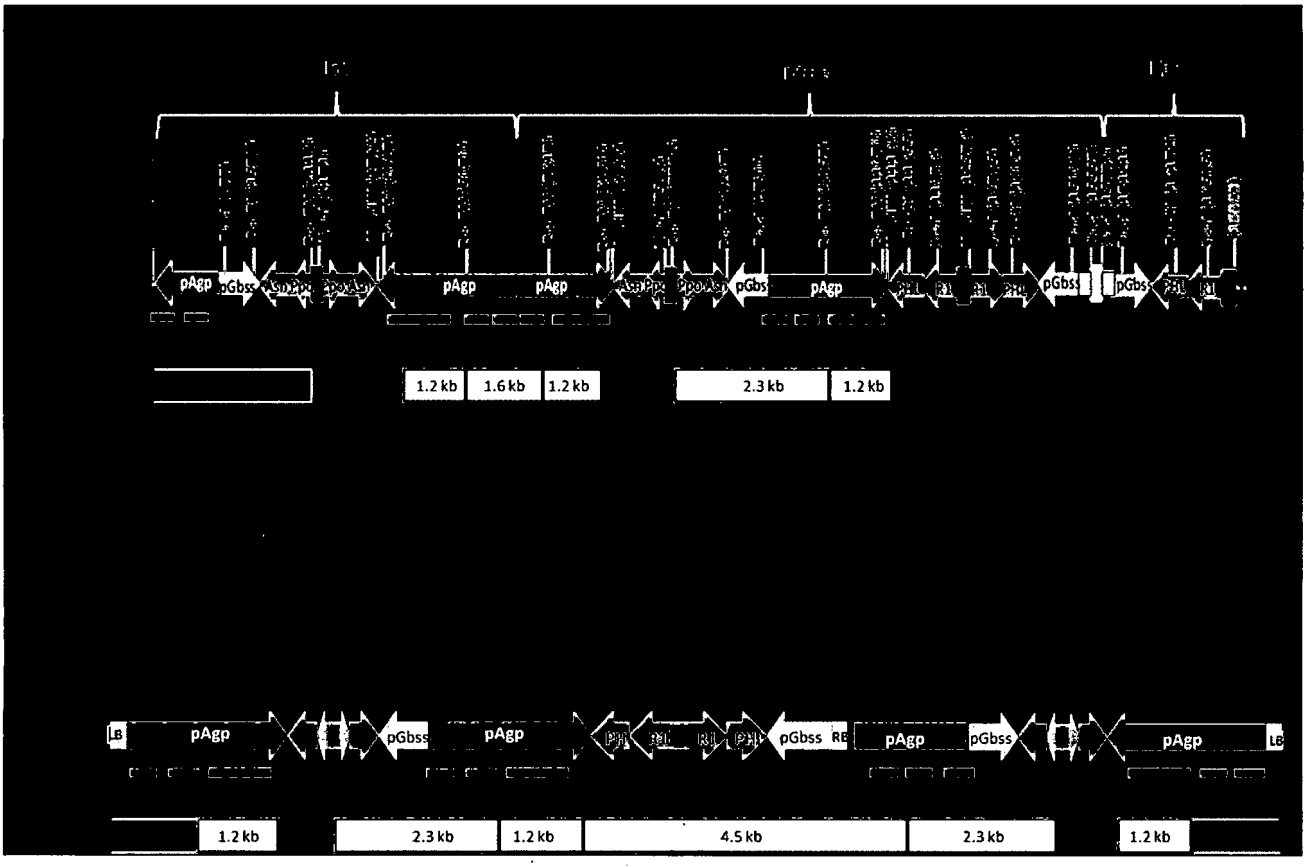
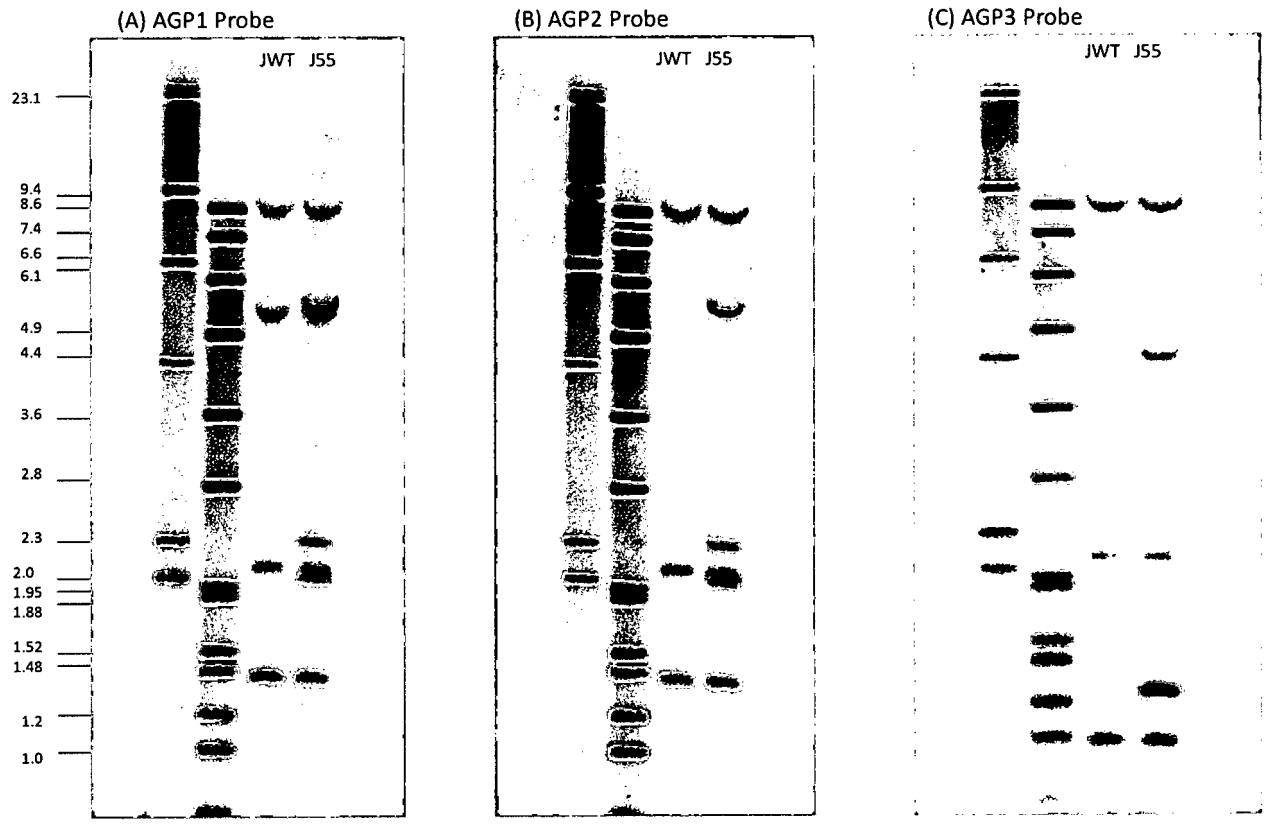


Figure D.4. Southern blots of J55 digested with EcoRV and hybridized with probes AGP1, AGP2, and AGP3



Genomic DNA was digested with EcoRV and hybridized with the (A) AGP1, (B) AGP2, or (B) AGP3 probe. JWT (Atlantic) and J55 (Atlantic J55). DigII and DigVII molecular weight markers are labeled adjacent to the blot on the left in kilobase pairs.

Supplement E: Bioinformatics Analysis of Inserts

The transformation process that introduces DNA into the genome of the potato has the remote potential to disrupt a native gene or introduce an unexpected toxin or allergen through expression of a novel open reading frame (ORF). This report describes our analysis of possible native gene disruption, toxicity, and allergenicity for four Innate™ potato events using the standard bioinformatics techniques summarized in Table 1.

Disruption of native genes and expression of unexpected toxins or allergens are all highly unlikely events, particularly in Innate™ potatoes that rely almost exclusively upon native potato DNA. In addition to promoter and enhancer elements, expression of unexpected proteins would require productive transcription through the insertion region with post-transcriptional processing producing a properly structured and polyadenylated messenger RNA transcript, followed by translation into a stable protein. Innate™ potato constructs include inverted repeats driven by opposing promoters, which limit transcriptional read through from either direction. The end result, by design, is small complementary RNAs or double-stranded hairpins that are processed by the RNA interference pathway into small interfering RNAs, preventing them from being translated. Nonetheless, we show the absence of allergenicity and toxicity potential of our events using a number of well-established bioinformatics techniques (Ladics, 2007; Goodman, 2008; Terrat, 2013).

Table 1: Overview of bioinformatics analyses

Analysis	Purpose	Approach
Stop-to-stop ORF Analysis	Identify all potential proteins that may be expressed by DNA insert and surrounding sequence.	ORF Finder: systematically identify all ORFs (≥20 amino acids) located between contiguous stop codons from all frames. Used for subsequent toxin and allergen analyses.
Allergenicity Analysis	Ensure that sequences capable of expressing known allergens have not been introduced by transformation.	AllergenOnline: find small regions of identity (8 amino acids) or larger regions of similarity (80 amino acid, ≥35% homology) with known allergens.
Toxicity Analysis	Ensure sequences capable of producing proteins similar to known toxins have not been introduced by transformation.	NCBI protein BLAST (blastp): identify proteins homologous to known toxins contained in target databases (E-value ≤ 1).
Native gene disruption	Verify that a novel protein has not been generated by integration within a native gene.	NCBI nucleotide BLAST (blastn): identify any native genes containing the flanking sequence as an indication of gene disruption.

RESULTS

Stop-to-stop ORF identification

Open reading frames (ORFs) can be identified as the contiguous sequence located between a canonical start codon and a downstream stop codon or, more generally, all sequence located between two stop codons in the same reading frame. As the latter definition will identify more ORFs, we used it as the basis for our analysis. The ORF Finder algorithm associated with the Sequence Manipulation Suite (Stothard, 2000) was used to identify all ORFs. As shown in Figure 1, the analysis of each event was performed using each insert with the known flanking sequences. The ORFs overlapping the known junction sites were included within each analysis. In total, each analysis spanned a region consisting of at least 11 kb of nucleic acid sequence for each event.

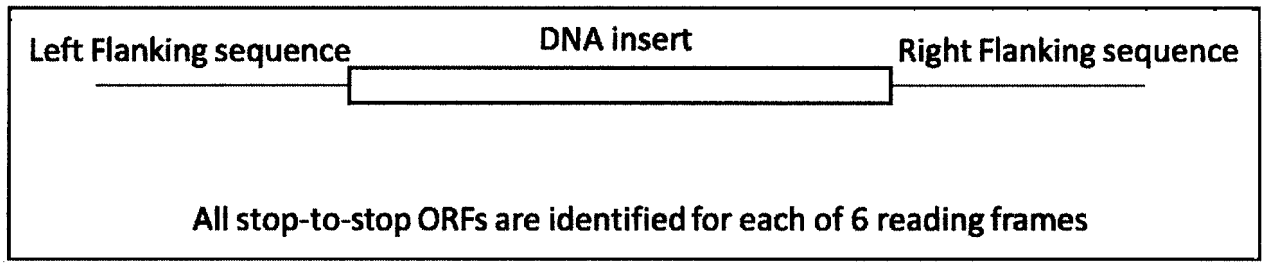


Figure 1. ORF Analysis Scheme

As many of the identified ORFs are replicates due to the redundant nature of the sequence contained within the DNA insert, the dataset was trimmed to only include unique ORF sequences. These ORFs were converted into a FASTA-formatted file and used for the subsequent toxicity and allergenicity analyses. As summarized in Table 2, we identified between 232 and 310 unique ORFs for the events.

Table 2 - Stop to Stop ORF Analysis Summary

Event	Number of ORFs	Mean ORF size (amino acids)	Largest ORF size (amino acids)
E12	232	37	182
F10	239	38	182
J55	289	36	182
J3	310	38	182

Allergenicity evaluation

The allergenicity potential of these ORFs (Table 2) was analyzed using a web-based tool (http://www.allergenonline.org/databasefasta.shtml) provided by the Food Allergy Research and Resource Program (FARRP). This tool allowed us to identify small regions (8-mers) of sequence identity between the ORFs found in each of the events and those of known allergens. These eight-amino acid matches could theoretically represent a B-cell or T-cell epitope, which is the part of the protein that is specifically recognized by the immune system (Metcalfe, 1996). The allergen database contains the sequence of known allergens, but the specific sequence responsible for allergenicity is not necessarily known, nor is it known whether an 8-mer is capable of inducing an allergic response (Goodman, 2008).

8-mer identity search

As shown in Table 3, a FASTA search led to identification of a single match between all events and a known allergen, endochitinase (GI:3201547) from *Persea Americana* (avocado). There were two independent ORFs containing this sequence within our construct because the open reading frame is contained within the GBS promoter native to the potato, which was coopted to drive expression of the silencing constructs contained in the insert. This polypeptide represents one of 319 distinct 8-mers in the full-length allergenic endochitinase protein, which makes it unlikely this particular 8-mer is responsible for the allergenicity. Further support is provided by the absence of the putative epitope from a database of known epitopes (http://www.iedb.org/). IgE cross reactivity has been observed between the endochitinase protein from avocado and latex proteins sharing a prohevein domain (Sowka, 1998). This particular domain does not include the N-terminal region containing the 8 amino acid, LPLLLLLL, motif identified in our search, which provides further evidence that this motif does not have known allergenic potential.

The presence of an ORF does not predict that it will be expressed, but if expressed it is not novel as the peptide sequence is present in many potato and human proteins. Collectively, these data suggest the peptide identified is a false positive and would not be a potential allergen, consistent with concerns over the high false-positive rate when looking for 8-mer matches (Goodman, 2008).

Table 3. Summary of Allergenicity Findings

Event	80-mer hits	8-mer hits	8-mer sequence	8-mer allergen target
E12	0	1	LPLLLLLL	endochitinase (GI:3201547)
F10	0	1	LPLLLLLL	endochitinase (GI:3201547)
J55	0	1	LPLLLLLL	endochitinase (GI:3201547)
J3	0	1	LPLLLLLL	endochitinase (GI:3201547)

80-mer homology search

A second analysis performed using the FARRP web-tool identifies larger regions of similarity between the ORFs and known allergens. This analysis compares all 80 amino acid sequences within an ORF and identifies any matches with greater than 35% homology to known allergens. The algorithm did not identify any potential allergens arising from ORFs found in any of the events or their flanking sequences (Table 3). Overall, no allergen-related safety concerns were identified for any of the Innate™ potato events.

Toxicity evaluation

Unlike with allergenicity studies, we are not aware of a formal method for establishing toxin-related safety in genetically-modified organisms, so we modeled our analysis after the rigorous approach used for the allergenicity studies. We consulted with experts at the National Center for Biotechnology Information (NCBI) and Uniprot to develop methods to generate and search toxin-specific databases for homology between our ORFs and known protein toxins. We took advantage of two repositories of annotated toxins for this analysis. The first database (mvirDB) consists of known bacterial toxins, virulence factors, and antibiotic resistance genes, which is a publicly-available repository maintained as a combination of at least eight independent database sources (Zhou, 2006). A second BLAST-compatible database was created to supplement the bacterial toxin database by extracting all eukaryotic proteins annotated as toxins within the Uniprot repository. These smaller and more specific databases make toxicity assessment more straightforward than non-specific searches against NCBI databases.

Table 4. Summary of Toxicity Database Queries

Event	mvirDB	uniprotToxin	NCBI nr
E12	0	0	1417
F10	0	0	2234
J55	0	0	2039
J3	0	0	2214

Using the blastp algorithm within the BLAST suite of applications available through NCBI, we analysed all of our ORFs against the NCBI non-redundant protein database (Table 4). Since the vast majority of the ORFs were small (35 amino acid average), many non-specific hits were generated making it a challenge to objectively assess toxicity although, as expected, most matches (E-value ≤ 1.0) were of potato origin. However, the blastp algorithm did not identify any proteins with significant homology when the more specific toxin databases were queried with the ORF sequences. Based on weak specificity, the potato origin of most matches within the NCBI database, and the lack of homology with the toxin database, no toxin-related safety concerns were identified for any of the Innate™ potato events.

Native gene disruption

The potato (*Solanum tuberosum*) genome presents some unique challenges for analysis of native gene disruption. Most potato cultivars are tetraploid, highly heterozygous, and include a significant amount of redundant/homologous DNA. These challenges have prevented the research community from sequencing the genome of these cultivars directly. Instead, they sequenced a unique homozygous form of the potato, a doubled monoploid, derived using tissue culture techniques (The Potato Genome Sequencing Consortium). This sequence was later used to integrate sequence from a heterozygous diploid line. Together, these efforts have provided a genome sequence that is valuable for investigating the evolution and genome organization of potatoes, but is still lacking for detailed analysis of individual loci in commercial cultivars, which are mostly tetraploid. It is not uncommon with BLAST to analyse known sequences against the current potato genome only to identify numerous hits scattered across chromosomes, or more perplexing, to retrieve no hits at all.

It is highly unlikely that a gene disruption would have a functional impact on the plant or tuber due to its tetraploid nature, which means that a single gene disruption would leave the plant with up to three functional copies of the native gene. These traits highlight the power of using biotechnology in potatoes as native gene disruptions are both uncommon and unlikely to result as a measurable or observable change in phenotype. In the event that a native gene is disrupted by an Innate™ construct, it is generally going to produce a truncated version of the native protein as opposed to a novel fusion protein since the ORFs contained in the construct are extremely short on average and would halt translation.

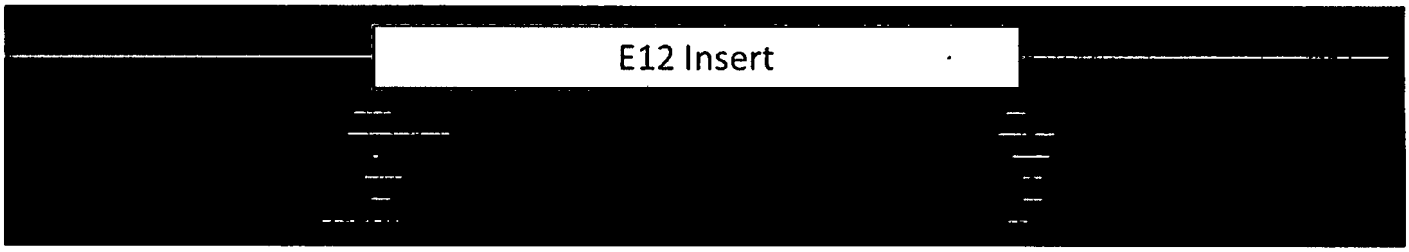
In an effort to identify the insertion site of the construct, we performed a BLAST (blastn) search against the NCBI and MSU potato genome databases to identify the likely insertion location and any annotated genes that may have been disrupted. When possible, the locus was further evaluated using the graphical viewers made available by NCBI and MSU to visually inspect the locus for disrupted genes. We also performed BLAST (blastx) searches, which translates the input nucleic acid sequences in all six reading frames and searches for protein matches. The results for each event are summarized below.

E12 Event

Despite many sequence matches, the most likely integration site appears to be on chromosome 12 (Figure 2). There is strong homology between the right and left flanking sequences identified with a locus on chromosome 12 (left flank, 56535700-56536479:56533662-56534963, right flank) according to the Michigan State University (MSU) genome database.

Neither the blastn nor blastx searches against the NCBI database identified annotated genes disrupted by the flanking sequences. A BLAST search against the "PGSC *S. tuberosum* group Phureja DM1-3 Transcripts (v3.4)" dataset revealed similarity to an expressed transcript, but that transcript maps to a different chromosome (chromosome 11) than the likely integration site (chromosome 12). Visual inspection of the tracks covering the locus on chromosome 12 using the MSU graphical genome browser did not identify any candidates for native gene disruption.

Figure 2. E12 insertion and junction open reading frames on chromosome 12



The open reading frames covering the junctions between the insert and the flanking sequences are shown in Figure 2 (not to scale). The sequences for the left (L1-L6) and right junction (R1-R6) open reading frames were analyzed and the results summarized in Table 5. No known toxins or allergens were associated with the ORFs covering the insert.

Table 5. Summary of toxicity and allergenicity analysis of ORFs at E12 insert junctions

Frame	ORF sequences	Toxins	Allergens
L1	CNNKFYIGENN**KRSVCG***	None	None
L2	ISTLSFIFTKFNVIINFILVRII**NEVCVVDPKSIVPLESVAMKDSLTYE ELPIEILDRQVRRLRKIEVASVTALWRSKGTKCLRQPKLKVGNQ TLSQRLYIQNGINIII***	None	None
L3	**	None	None
L4	**RYDRFWINHTHFVY**YSHQYKIYYYIKFGEYK*	None	None
L5	**ILDQPHTLRL**LFSPI*	None	None
L6	**VRLSFIATLSKGTIDFGSTTHTSF**IILTNIKFIITLNLVNINDRVEIHLV NINKNEGSNTFLIFHNKKKRLNLMTKHNIDKRQFSLAVPHFLNLSI RKMFVHMTEEYQVQLIEDLGKI*	None	None
R1	**ALYRVGLRSVTL**Y*	None	None
R2	**IIISGAHRYAINFIYLVGSRLYTELDYGQSL**CTSKDLFLSILSSYIKSF KEILRVREWKKHVNSE*	None	None
R3	**LGVGFIPSWTTVSHF**VLVKICFYPFYLLISNHSRKY*	None	None
R4	EDKMDKNRSLLV**QSD***	None	None
R5	KQIFTST**K***	None	None
R6	Y**KVTDRSPTRYKAYSQLNI***	None	None

- Open reading frames are shown for all junctions. Bold sequence refers to insert DNA and non-bolded sequence is plant.

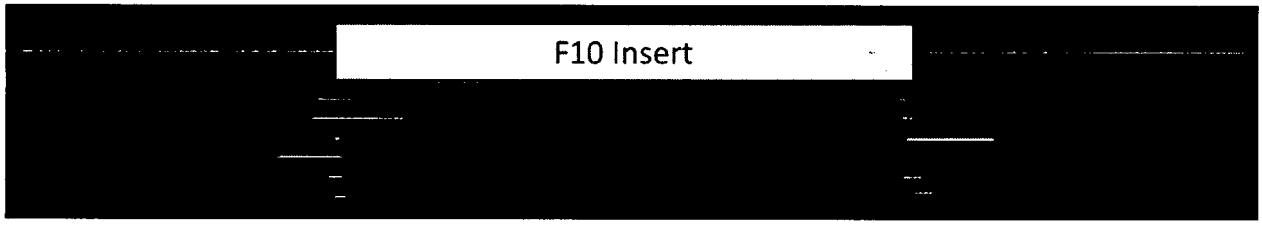
Since there is no evidence of a native gene disruption, no known allergens or toxins associated with the ORFs, and no unexpected differences in composition or agronomy, there is no evidence of a safety concern with E12.

F10 Event

As with the E12 event, both the left and right flanking sequences were determined for the F10 insert. Although there are numerous high quality matches using the MSU potato database, the most likely integration site is on chromosome 8 (left flank, 49751958-49752732:49750820-49751488, right flank).

When a BLAST search is performed against the transcripts cloned from potato, there is similarity to a transcript, PGSC0003DMT400045203, which is annotated as a putative gene. Although it is possible that a native potato gene has been disrupted by the F10 insertion, we did not find any evidence that this pseudogene actually encodes a functional protein.

Figure 3. F10 insertion and junction open reading frames on chromosome 8



The open reading frames covering the junctions between the insert and the flanking sequences are shown in Figure 3 (not to scale). The sequences for the left (L1-L6) and right junction (R1-R6) open reading frames were analyzed and the findings summarized in Table 6. No known toxins or allergens were associated with the ORFs at the insert site.

Table 6. Summary of toxicity and allergenicity analysis of ORFs at F10 insert junctions

Frame	ORF sequences	Toxins	Allergens
L1	SYNNNWSSSHQLVQ**QDIYRCKRSVCG**	None	None
L2	ATLVKDEAITITGPAAISWSS**RIYTGVNEVCVVDPKSIVPLESVA MKDSLTYEELPIEILDRQVRRLRKIEVASVTALWRSKGTKCLRQP KLKVGNQTLSQRLYIQNGINIII***	None	None
L3	LVQQPSTGPAGYIP**V***	None	None
L4	**VRLSFIATLSKGTIDFGSTTHTSFTPVYI**LLDQLMAAGPVIVIASSF TNVAYERLPLEEDGNTQGSDGGGDGVVNNNPFSDPSNDGLPFF NLPLNMPNCFNPGSASVDGWVGNPSLRPPFGV*	None	None
L5	**RYDRFWINHTHFVYTGIYP**AGPVDGCWTSYCYSFIFY*	None	None
L6	**ILDQPHTLRLHRYIS**CWTS*	None	None
R1	**LGINLVHQPKI***	None	None
R2	**VISLLCGHQFS**WASI*	None	None
R3	**VSSVGINLV**GHQFSPPAKNIVKLVAPGGAGGGKNEPLSDKISNR PFNVTTDEELILPVLLLLPVLVGCLILTLVTIPLPLNIQIPRCLRLAYD DIHSNTSHPLPISRICARNVFALSLVIITGGFGLFLDPGGRPLGLRP TRSPGPDEFAPTRSN*	None	None
R4	IDAQ**LN***	None	None
R5	CP**TKLMPTEETYNLQGHVVLGLESD***	None	None
R6	WFVFTTTSTTRGNKFDYIFGWWTKLMP**N***	None	None

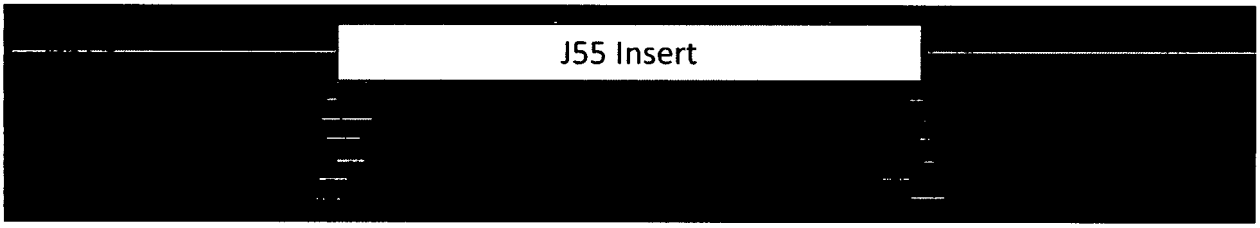
- Open reading frames are shown for all junctions. Bold sequence refers to insert DNA and non-bolded sequence is plant.

Since these potatoes are tetraploid, the F10 potato has three unmodified copies of the putative gene so a disruption is unlikely to have an effect on the potato itself. The compositional and agronomic data were consistent with this conclusion as the only measurable differences between the F10 event and its commercial parent were those targeted by the gene silencing cassette. Since the bioinformatics analysis did not find any evidence of a potential toxin or allergen created by the insertion, there is no evidence of a safety concern associated with the putative gene disruptions in F10.

J55 Event

Unlike with the other events, there were very few matches between the J55 flanking regions and the potato genome when analyzed using MSU's potato database as there are major sequence differences between the published sequence and Atlantic varieties. The search results suggest the insertion integrated on chromosome 4 (left flank,9547964-9549110:9549165-9550321, right flank). Similar to F10, this integration appears to fall within a gene of unknown function (PGSC0003DMG400027260).

Figure 4. J55 insertion and junction open reading frames on chromosome 4



The open reading frames covering the junctions between the insert and the flanking sequences are shown in Figure 4 (not to scale). The sequences for the left (L1-L6) and right junction (R1-R6) open reading frames were analyzed as described above and are summarized in Table 7. No known toxins or allergens were associated with the ORFs covering the insert.

Table 7. Summary of toxicity and allergenicity analysis of ORFs at J55 insert junctions

Frame	ORF sequences	Toxins	Allergens
L1	KSTSN*	None	None
L2	LVFSRRIWTENQQAI**EELPIEILDRQVRRLRKIEVASVTALWRSK GTKCLRQPKLKVGNQTLSQRLYIQNGINIII***	None	None
L3	SNSQLESNLSFPEEFGLKINKQL**KNYLLRFLIVRSEG***	None	None
L4	**RSRISIGSS**SIAC*	None	None
L5	**FF**NCLLIFSPNSSGKDKLDSS*	None	None
L6	**VVL**QLLVDFQSKFFWKRQVRF*	None	None
R1	**VRL**CVKLSGCFSDMTQLP*	None	None
R2	**FFISET**MRETFRLLLRYDTTTLRSSF*	None	None
R3	**DY**A*	None	None
R4	KFHA*	None	None
R5	PQGSCVISEKQPESFTH**SLTYEELPIEILDRQVRRLRKIEVASVTAL WRSKGTKCLRQPKLKVGNQTLSQRLYIQNGINIII***	None	None
R6	YMKNSSFTYQKDDLKVVVSYLRSNLKVSR**IVSLMKNYLLRFLIVRS EG***	None	None

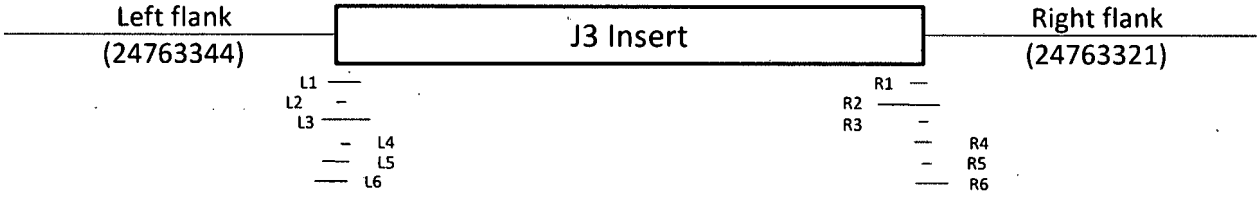
- Open reading frames are shown for all junctions. Bold sequence refers to insert DNA and non-bolded sequence is plant.

Since this tetraploid event contains three unmodified copies of the disrupted gene, no allergens or toxins are associated with the ORFs, and no unexpected differences in composition or agronomy were identified, there is no evidence of a safety concern with J55.

J3 Event

According to the MSU genome browser, the chromosomal insertion site was 862 bp upstream of a putative gene/transcript of unknown function (PGSC0003DMT400095935) on chromosome 6. Protein BLASTs against the NIH database did not reveal any likely protein functions for the 128 amino acid, putative polypeptide encoded by this transcript. As the insert did not disrupt the transcript, it would not result in a novel fusion protein or a modified version of the native protein. Furthermore, BLASTs against the MSU transcript database did not identify any evidence of other transcripts derived from this locus that could be disrupted.

Figure 5. J3 insertion and junction open reading frames on chromosome 6



The open reading frames covering the junctions between the insert and the flanking sequences are shown in Figure 5 (not to scale). The sequences for the left (L1-L6) and right junction (R1-R6) open reading frames were analyzed and the results summarized in Table 8. No known toxins or allergens were associated with the ORFs at the insert site.

Table 8. Summary of toxicity and allergenicity of ORFs at J3 insert junctions

Frame	ORF sequences	Toxins	Allergens
L1	PHIYFCSIISSIRVIDIDQNRYSNLQQDNHKL**GNSHAMK***	None	None
L2	***ETHML***	None	None
L3	SKPVLKFATGQPQAR**KLTCYEINSHLTTP***	None	None
L4	***SV***	None	None
L5	*RYQDFGTSLNAVPCGCAL**FSVH**	None	None
L6	*FRYEFKCCSLWLSP**FECAIFYI**	None	None
R1	*KSPRI**NFFWKGQKSFTIKSKEPQAQASTKAV**	None	None
R2	*FDEKALEL**IFFGRVKNHLQLKARSHKLKHPQKQCKNTIFS LKPKYKQNRNYEYRTKGEPHPTTNKSNLSSNANKNIIYTS QNKSKTGRELKRGSCLRSRSIFLGISARCISLDLGISAVHLSG LGPQYLGSPQKEQHYQTH**	None	None
R3	***FFLEGSKIIYN***	None	None
R4	*MQKIFFAKFKLKEPQNSSFARSN**IKKPLTLF**	None	None
R5	***NKKSPDFIM**	None	None
R6	***NSIKKQRNSELPKFNSNKCKNSSFPRLNSNKRNIQHFLGLI LKKQFP**	None	None

- Open reading frames are shown for all junctions. Bold sequence refers to insert DNA and non-bolded sequence is plant.

Since the insert did not disrupt a gene, no allergens or toxins are associated with the ORFs at the junctions, and no unexpected differences in composition or agronomy were observed, there is no evidence of a safety concern for J3.

MATERIALS AND METHODS

ORF detection

All potential open reading frames (ORFs) created as a result of the event-specific, integration event were identified using the ORF Finder web application (Stothard, 2000) available through the Sequence Manipulation Suite (http://www.bioinformatics.org/sms2/orf_find.html). The search parameters were defined to identify all ORFs with at least 20 amino acids located between two contiguous stop codons. A nucleotide sequence has the potential to be translated in up to three reading frames consisting of contiguous codon triplets from RNA transcribed from either direction on the chromosome. All six open reading frames were analyzed to identify ORFs using the insert sequence and flanking plant genomic sequence on each side. The 500 nucleotides of flanking sequence is more than enough to account for any potential ORFs encompassing the junction sequences. The results were converted into FASTA-formatted files for further analysis.

Database and software resources

The most recent Blast software suite (v2.2.28; Altschul, 1997) was downloaded from NCBI (ftp://ftp.ncbi.nlm.nih.gov/blast/executables/blast+/LATEST/) and installed locally. A number of BLAST-compatible databases were generated and/or downloaded to support the toxin analysis described herein. The most recent NCBI non-redundant (nr) protein database (August 26, 2013 post date) was downloaded using the update_blastdb.pl script provided with the BLAST application suite. Searches against this database are comprehensive, but non-specific and produce data that can be challenging to associate with putative toxins. In order to perform more directed searches, we took advantage of two toxin-specific resources. The first is a microbial database of toxins, virulence factors, and antibiotic resistance genes (Zhou et al., 2006) that was downloaded from the Lawrence Livermore National Laboratory Virulence Database Home Page (http://mvirdb.llnl.gov/) and installed locally (mvirdb). This database comprises known microbial protein toxins from numerous publically available sources, including Tox-Prot, SCORPION, PRINTS, VFDB, TVFac, ARGO, and VIDA. A second eukaryote-specific (taxid: 2759) toxin database was generated by downloading all FASTA-formatted sequences annotated with the keyword=toxin from the uniprot database using a browser script provided by Uniprot technical support at the SIB Swiss Institute of Bioinformatics:

http://www.uniprot.org/uniprot/?query=taxonomy%3a2759+keyword%3atoxin&force=yes&format=fasta&include=yes

This toxin dataset was converted into a BLAST-compatible database (uniprot_toxin) using the makeblastdb.exe utility provided in the BLAST software suite.

Allergenicity database searches

Allergenicity potential was evaluated using the public, allergen-specific search engine (http://www.allergenonline.org/databasefasta.shtml) available through the Food Allergy Research and Resource Program at the University of Nebraska. The ORFs associated with the insert and flanking regions were analyzed using two approaches: (1) 80-mer sliding region homology search and (2) 8-mer identity search. Only protein sequences consisting of 28 or more amino acids were analyzed using the 80-mer sliding window as this is the minimum sequence size capable of reaching the lower threshold target of 35% homology. However, all ORFs were analyzed using the 8-mer match. All searches were performed using database version 13, dated February 12, 2013.

Toxin database searches

The comprehensive set of ORFs predicted by the ORF Finder application was used as input for BLAST (blastp) searches against the databases described above. When performing blastp searches it is common to consider the Expect value (E-value) as a measure of statistical significance where values less than 0.1 or 0.05 are generally considered biologically significant (BLAST help). That is, the E-value describes the number of hits that one might "expect" to see by chance when searching a database of a particular size. In order to consider any potential homology between the ORFs and the sequences in the toxin-specific databases, we analyzed our BLAST searches using a higher E-value threshold of 1.0. However, since the E-value calculation is dependent upon the size of the search space, we consulted with a BLAST application expert at NCBI to determine the appropriate search space (–searchsp) parameter for our toxin database searches. BLAST reported an effective search space of roughly 1×10^{11} when the ORFs were compared to (blastp-short) the NCBI nr database. Thus, our database searches used the following command line input:

>blastp –task blastp-short –query ORFs.fa –db database –out db_output.txt –searchsp 100000000000 –outfmt 6 –evalue 1.01

The *database* string was replaced by nr, mvirdb, or uniprot_toxin depending on the specific search. The nr searches served as a control to ensure our searches were performing as expected. The algorithm applies the PAM30 scoring matrix with gap penalties of 9 for existence and 1 for extension as a default associated with the blastp-short search parameter.

Native gene disruption

Where available, the sequences identified as the left and right flanking regions were used as input for a BLAST (blastn) search against the NCBI potato genome to identify the likely integration site and any genes associated with the flanking regions (E-value cutoff of 1×10^{-6}). The same sequences were used to search the more frequently updated potato genome housed at Michigan State University (MSU) (http://potato.plantbiology.msu.edu/integrated_searches.shtml). All searches were performed against the most recent version of the database (v 4.03). The sequences were also provided as input for BLAST (blastx) searches to identify any homologous proteins to the nucleotide coding sequence. This algorithm compares the translational products of the nucleotide sequence from

all six reading frames to proteins in the database. These searches were also performed against the NCBI potato database (E-value cutoff of 0.01).

CONCLUSIONS

Using a number of well-established bioinformatics tools, we have performed a comprehensive analysis on the insert and flanking regions of the Innate™ potato events: E12, F10, J55 and J3.

Although F10 and J55 are predicted to have inserts disrupting a putative native gene according to genome annotation, each of these lines is derived from a commercial tetraploid variety. Thus, each of these events contains three unmodified copies of the native genes and exhibit no unexpected differences in agronomy or molecular composition. Furthermore, neither the allergenicity nor toxicity analyses uncovered any potential safety concerns associated with any of these events, including the junction regions. This is not surprising considering the source of the DNA used in the Innate™ potato events is almost exclusively derived from the host, potato.

Collectively, our bioinformatics studies did not identify any safety concerns associated with any of the events as a result of the transformation.

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s.20(1)(b)
s.20(1)(c)

Jaimie Schnell - Fwd: RE: Request for additional information for MON 87411

From: Sarah G. Davis
To: Schnell, Jaimie
Date: 2015-02-24 3:42 PM
Subject: Fwd: RE: Request for additional information for MON 87411
Attachments: Cover letter for Response to Jan-16-2015 NTO DL.pdf; MSL0023893_DvSnf7 MON8741 and 87411 greenhouse .pdf; MSL0025423_CRW3 US DRA.pdf; MSL0026256_Fridley.pdf; Response to Jan-16-2015 NTO DL.pdf

Hi Jaimie,

I'm not sure if Agnes or Nicole already forwarded this to you, but here's Monsanto's NTO response for MON 87411. I've started reviewing it today, although given it's size, it's unlikely I'll be able to make significant headway. Nevertheless, I can help out even after I'm gone. We can touch base tomorrow on a few things, this included.

Sarah

>>> 2015-02-20 1:29 PM >>>

Hi Sarah,

Please find the attached cover letter and information in response to the CFIA deficiency letter from January 16 pertaining to the non-target organism safety assessment of MON 87411.

In addition, I have attached the following Monsanto studies in support of our response:

Hard copies of these documents will be delivered to your office today. Please feel free to get back to me with any additional questions.

Best regards,

t. |
c. |
f. 613.234.2063

Monsanto Canada Inc.
180 Kent St. Suite 810
Ottawa, ON
K1P 0B6

www.monsanto.ca

From: Sarah G. Davis [mailto:Sarah.Davis@inspection.gc.ca]
Sent: Friday, January 16, 2015 12:23 PM
To:
Cc: Agnes Lichota; Michele McMillan; Nicole van der Lee; Philip Macdonald
Subject: Request for additional information for MON 87411

Hi

Please see attached for a request for additional information pertaining to the non-target organism safety assessment of MON 87411. A hard copy has been placed in the mail.

Also, please note that today is Michele's last day at the Agency, as she's accepted a new position with Statistics Canada. If you could share this news with your colleagues, it would be greatly appreciated.

Sincerely,
Sarah

Sarah Davis, M.Sc.

Senior Risk Assessor - Biotechnology, Plant and Biotechnology Risk Assessment Unit
Canadian Food Inspection Agency / Government of Canada
Sarah.Davis@inspection.gc.ca/ Tel: (613) 773-5271

Évaluatrice principale des risques - biotechnologie, Unité d'évaluation des risques des végétaux et produits de la biotechnologie
Agence canadienne d'inspection des aliments / Gouvernement du Canada
Sarah.Davis@inspection.gc.ca / Tél: 613) 773-5271

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Date: 2015-02-23 9:02 AM
Subject: Fwd: RE: Request for additional information for MON 87411
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Hi Jamie,

It looks like you were not cc'd on email.

Cheers,

Agnes

>>> 2015-02-20 1:29 PM >>>

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MONSANTO

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REGULATORY AFFAIRS
180 KENT STREET
SUITE 810
OTTAWA, ON K1P 0B6
PHONE (613) 234-5121
FAX (613) 234-2063

February 20, 2015

Sarah Davis
Plant and Biotechnology Risk Assessment Unit
Canadian Food Inspection Agency
1400 Merivale Road
Ottawa, ON K1A 0Y9

Re: Response to NTO Deficiency Letter of January 16, 2015 (MON 87411)

Dear Ms. Davis,

In response to the request for additional information on non-target organisms, please find the questions and Monsanto responses following this cover letter.

As requested following the CFIA/Monsanto WebEx meeting of February 9, 2015, electronic and CD copies of the following Monsanto studies have been submitted on February 10, 2015:

In addition, Monsanto is providing electronic and hard copies of the following supporting studies:

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If you have any questions concerning this information, please contact this office at your convenience. Since this information, in the opinion of Monsanto Company constitutes trade secrets and/or confidential or proprietary information, we request that government officials treat this information accordingly.

Sincerely,
MONSANTO CANADA INC.

/Encl.

cc. Monsanto Company

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From: Sarah G. Davis
To: Lichota, Agnes; Schnell, Jaimie
Date: 2015-03-03 10:03 AM
Subject: Fwd: Simplot responses to CFIA PBRA dated September 2, 2014
Attachments: 27Feb15 CFIA_PBRA final response.docx

Hi there,

Simplot has sent an agronomy/NTO response! I haven't looked at the attachment just yet. I'll start reviewing the NTO portion this week. Agnès, we can sit down and discuss Michele's agronomy assessment if you'd like? She has very detailed review notes that are linked in the biotech tracking sheet.

Sarah

>>> 2015-02-27 7:08 PM >>>

Attached please find Simplot's response to the combined CFIA PBRA letter dated September 2, 2014, regarding questions for the E12, F10, J3 and J55 potato events with low acrylamide potential and reduced black spot bruising (submission file # 4000310).

On Monday, we will overnight a signed hard copy of this response, including a CD with PDFs of all the references cited.

As I explained in the cover letter, I truly apologize for the length of time it has taken us to respond. We intend to be much more prompt in our responses going forward.

Please let us know if you have any questions.

Best regards,

Simplot Plant Sciences
Tel.
Mobile

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Simplot
Plant Sciences

J.R. Simplot Company 5369 W Irving St Boise ID 83706

February 24, 2015

Plant and Biotechnology Risk Assessment Unit
Canadian Food Inspection Agency
1400 Merivale Road
Ottawa, Ontario K1A 0Y9
Attention: Michele McMillan and Sarah Davis

Re: J. R. Simplot Company's application for unconfined release of Innate™ potatoes with low acrylamide potential and reduced black spot bruise; events E12 (Russet Burbank); F10 (Ranger Russet); J3 and J55 (Atlantic); Submission File # 4000310

Simplot response to CFIA PBRA Environmental questions dated September 2, 2014

Dear Ms. McMillan and Ms. Davis,

This letter is in response to your letter of September 2, 2014, requesting additional information regarding the assessment of the agronomic and non-target organism data that was provided in the application.

Please find the responses to your questions on the following pages. I sincerely apologize for the length of time it has taken us to respond. My predecessor, Pete Clark, left Simplot last fall and his position was not filled until I started with the company earlier this month. These Innate™ potato events continue to be important, and we would like to continue with the CFIA PBRA environmental review and authorisation process.

For future reference, here is my contact information:

J.R. Simplot Company
5369 West Irving Street
Boise, ID 83706
Tel:
Mobile: (
Fax: (208) 780-6027
Email:

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Please do not hesitate to contact me if you have any further questions or concerns.

Sincerely,

cc: Robert Potter Consulting

Table of Contents **Pages**

Responses to Questions

1. Page 17 of the main application notes that according to Statistics Canada (2012), the highest producing province in 2011 was Prince Edward Island (23.9 million cwt), followed by Manitoba(17.5 million cwt), Alberta (16.6 million cwt), New Brunswick (11.9 million cwt), Quebec (11.4million cwt), Ontario (6.4 million cwt), Saskatchewan (2.0 million cwt), British Columbia (1.7million cwt), Nova Scotia (0.5 million cwt), and Newfoundland and Labrador (0.09 million cwt). Given that the agronomy and disease susceptibility studies described in the application did not include any Canadian sites, please provide an expanded scientific justification as to how the data collected from your studies are applicable to Canada's potato-growing regions. Include references to soil type, climatological data, standard regional agronomic practices, pest and beneficial organisms found in the region, etc. Please make specific reference to where each variety was tested in relation to the main growing regions for those varieties within Canada. If you cannot justify the relevance of one or more of your study sites, please remove it/them from the analyses.

References:

- **Statistics Canada. 2012. Canadian Potato Production, vol. 9, no. 3. http://www.statcan.gc.ca/pub/22-008-x/22-008-x2012001-eng.htm (accessed 26 August 2014)**

Response: Please see Supplement A, entitled "Agronomic Practices: Comparison between U.S. and Canada" for a report that discusses the applicability of various U.S. field trial locations, many of which are the same as or similar to the locations used to generate the agronomy and disease studies in the application (Table 14 on page 118 of the original submission), to Canadian regions.

This report was prepared by Context Network (Context) for the J. R. Simplot Company and clearly identifies those Canadian regions that share the highest degree of commonality with Simplot field trial locations (see table below). This document compares the Canadian and certain U.S. potato-growing regions based on various factors, such as potato varieties grown, soil types, pests, fertility practices, agronomic practices, and climate conditions. Although this report was written specifically for another biotech event, W8, the comparison of agronomic practices should be equally valuable for events E12, F10, J3, and J55.

Simplot Field Trial Locations and Most Similar Canadian Potato Production Regions

U.S. Simplot Field Trial Locations (Number of agronomy and disease sites over years in original submission, from Table 14 of the original submission)	Most Similar Canadian Potato Production Region
Michigan (4) Wisconsin (7)	Quebec and Ontario
North Dakota (2)	Manitoba
Idaho (6) Washington (2)	Alberta and Saskatchewan
Florida (3) Indiana (1) Nebraska (1)	Not analyzed

Of the 26 sites that comprised the agronomic and disease field data, 20 of them are in regions that have a high degree of similarity to Canadian potato production regions. Four of the sites (in Florida, Indiana, and Nebraska) were not included in the Context analysis of sites and may be less similar to Canadian potato production regions. However, these four sites represent a minority of the 26 total locations and, upon specific examination, did not appear to generate data that was out of the ordinary from the other 20 sites (data not shown). To remove them from the study and re-analyze the data would represent a significant amount of work and would likely not result in a different overall conclusion of agronomic similarity between the various events and their controls.

The Context report supports our conclusion that potato production in the Northern U.S. and Canada is contiguous and there is similarity in potato varieties grown, soil types, pests, fertility practices, agronomic practices, and climate conditions. Because of the similarity of the majority of U.S. field trial locations to various Canadian potato production regions, the data from Simplot field trial locations are applicable to Canada's potato-growing regions.

2. Please provide more details for the following phenotypic rating scales listed on pages 122 and 123 of the main application: insect stressors, disease stressors, abiotic stressors, plant vigor, foliage color, leaflet size, leaflet curl, vine size, and vine maturity. For example, please describe how the observer would have differentiated a 1 from a 2 or a 4 from a 5.

Response: Below are clarified rating scale descriptions for the attributes listed above. These are also noted in the footnotes of the updated Table 15 below.

1 to 5 scale for vigor, color, leaflet size, curl, vine size, and vine maturity:

- 1 = severely less than the varietal average;
- 2 = noticeably less than varietal average, but not severe;
- 3 = plants are similar to the varietal average;
- 4 = slightly more than varietal average;
- 5 = obviously more than the varietal average.

1 to 5 scale for insect, disease, abiotic, stressors:

- 1 = severe damage;
- 2 = above moderate damage;
- 3 = moderate damage for population;
- 4 = slight damage observed;
- 5 = no damage.

3. Footnote 2, located at the bottom of table 15 on page 122 of the main application, notes that while it was expected that all controls would have mean values of 3, some observers treated the scale as if 3 were normal, rather than a comparison to the control. Please provide a scientific justification as to how these two types of data can be combined in the same analysis. If a valid scientific justification cannot be made, please analyze the data obtained using one method separately from the data obtained using the other method.

Response: Footnote 2 has been deleted (see updated Table 15). It was expected that controls and the varietal average would typically be the same.

Updated Table 15. Agronomic Characteristics Evaluated

General characteristic	Characteristic measured	Evaluation timing[1]	Data description	Scale[2,3]
Early Emergence	Emergence	30 days after planting	% emergence	Percent based on number of seed pieces planted
Final Emergence	Emergence	Early season	% emergence	Percent based on number of seed pieces planted
Insect Stressors	Population	Early, Mid, & Late season	Visual estimate of relative population	1 to 5 point scale
Disease Stressors	Symptoms	Early, Mid, & Late season	Visual estimate of relative pressure	1 to 5 point scale
Abiotic Stressors	Symptoms	Early, Mid, & Late season	Visual estimate of relative symptom expression	1 to 5 point scale
Stems Per Plant	Stems per Plant	Early season	Count of stems per plant	Number of stems per plant
Incidental Stressors	Diseases	Mid & Late season	Observations	Presence/absence
	Insects	Midseason	Observations	Presence/absence
Above ground characteristics	Plant Vigor	Midseason	Visual estimate of relative vigor	1 to 5 point scale
	Foliage Color	Midseason	Visual estimate of relative foliage color	1 to 5 point scale
	Leaflet Size	Midseason	Visual estimate of relative leaflet size	1 to 5 point scale
	Leaflet Curl	Midseason	Visual estimate of relative leaflet curl	1 to 5 point scale
	Flower Color	Midseason	Observation of flower color	Flower color recorded as purple, white, or mixed per plot
	Senescence	Late season	Visual estimate of % necrotic foliage at maturity	% of necrotic vine per plot
	Vine Size	Late season	Visual estimate of relative vine size	1 to 5 point scale
	Vine maturity	Late season	Visual estimate of relative vine maturity	1 to 5 point scale
Yield	Total yield	After harvest	Plot weight	Lbs./row of 20 seed pieces
	Tuber grading	After harvest	Tubers categorized as 4-6 oz., 6-10 oz., 10-14 oz., >14 oz., U.S. #1, Grade B, Grade A, Oversize, or Pick Out, as appropriate	% of tubers by weight in each category
	Specific gravity	After Harvest	Tuber sample weight in air/(weight in air - weight in water)	Numeric specific gravity value
	High Sugar	After Harvest	Color rating of test fried strips based on USDA Color Chart for French Fried Potatoes	% of tubers with >1/2 of the fried strip has a number 3 or darker color
	Sugar ends	After Harvest	Color rating of the end of test fried strips based on USDA Color Chart for French Fried Potatoes	% of tubers with an end ¼" long or longer on the darkest end of the strip, testing number 3 or darker color
	Total Internal Defects	After Harvest	Sum of internal defects such as hollow heart, vascular discoloration, brown center, etc.	% of internal defects

[1]Early season observations were made at approximately 45 days after emergence. Midseason observations were made during the early bloom stage. Late season notes were taken during the crop senescence stage.

[2] 1 to 5 scale for vigor, color, leaflet size, curl, vine size, and vine maturity. 1 = severely less than the varietal average, 2 = noticeably less than varietal average, but not severe, 3 = plants are similar to the varietal average, 4 = slightly more than varietal average, 5 = obviously more than the varietal average

[3]1 to 5 scale for insect, disease, abiotic, stressors. 1 = severe damage, 2 = above moderate damage,

3 = moderate damage for population, 4 = slight damage observed, 5 = no damage

4. The agronomic data and stressor observations presented in Section 7 of the main application and Appendix 6 were grouped across sites and across years prior to statistical analyses, which could mask differences in agronomic performance resulting from regional environmental differences. Please provide additional analyses for data collected from each site and year separately.

Response: As requested, the agronomic data were re-analyzed by site. Please see Supplement B.

Stressor observations are categorical data and, as stated in the footnotes of Tables 22 and 23 of the original submission, were not statistically analyzed. The ranges for each event and its control were compared, and a difference was identified when the range of the event was outside the range of the control. When differences were observed, details were included in the footnotes identifying the site, year, and range of values observed for the event and its control.

5. The rating scales used for assessing insect stressors, disease stressors, abiotic stressors, plant vigor, leaflet size, leaflet curl, vine size, and vine maturity are ordinal scales (pages 122-123 of the main application). No analyses have been provided to demonstrate that the ordinal data from these observations follow a normal distribution. If the data does not meet the assumption of normality, it is statistically inappropriate to use parametric statistics to analyze the results. Please either provide analyses to indicate that the observations follow a normal distribution or reanalyze the data for the above agronomic characteristics using an appropriate non-parametric test.

Response: Of the attributes mentioned, insect, disease, and abiotic stressors were not statistically analyzed.

The model used to analyze the data was a mixed model containing both fixed and random effects. A separate analysis was done for each potato variety. The parametric model used is given by: $y_{ijkl} = \mu + Year_i + Location\ (Year)_j + Rep\ (Year\ Location)_k + Treatment_l + (Year*Treatment)_{il} + (Treatment*\ Location(Year))_{ijl} + \varepsilon_{ijkl}$, where Year, Location (Year), Rep (Year Location), Year*Treatment, Treatment*Location(Year), and ε are all random effects. Treatment is a fixed effect and y represents the data values for combinations of Year, Location, Rep, and Treatment.

A nonparametric test does not exist for a mixed model containing both fixed and random effects. Thus, a parametric model was fit and the residuals from the model were examined for violations of the ANOVA assumptions. In a mixed model the assumptions of normality and equal variance are on the residuals and not the observations. The residual plot should have values fluctuating around zero with no trends if none of the ANOVA assumptions are violated. Since the ANOVA is robust to non-normality as long as symmetry exists the residual plots are also examined for symmetry. In most cases the residual plots did not indicate any violations of the assumptions. For the cases where the residual plot was not fluctuating around zero in a random fashion it was because most of the data values were identical and there were more values on one side of the zero line then the other (either positive or negative). Thus, the treatment means were similar and a statistical test is superfluous.

A review of the residual plots revealed that plant vigor for all varieties, leaflet size for Ranger, and leaflet curl for Ranger all met the assumptions for the ANOVA analysis. The residual plots for foliage color for Burbank and Atlantic, leaflet size for Burbank and Atlantic, and leaflet curl for Burbank may be questionable. Some p-values for these characteristics were not provided due to the lack of variability in the data. As stated in Section 7.5 of the main application, every effort was made to generate p-values to aid in the interpretation of the data. Some departures from the assumptions of normality and equal variances were allowed since the results were always interpreted in the context of variation observed in the combined control range. It is our recommendation that the focus always be placed on the means, combined control range, and biological significance. The p-values provided are intended to aid in the assessment but are not absolute indicators of biological significance.

6. According to Section 7.6 of the main application, two different methods were used to evaluate insect, disease, and abiotic stressors:

a. In 2009 and 2010 the principal investigator was instructed to record the presence or absence of insect, disease, and abiotic stressors. Please indicate in more detail how these observations were made. For example, were the observations made at one or several points throughout the season? Were these observations made at every study site? Were all plants thoroughly examined for each incidental stressor or were a certain number of plants randomly selected from the plot? Did the investigator make any attempt to identify the insects/diseases? Please include any other relevant details.

Response: Data collected on stressors in 2009 and 2010 were obtained by asking the Principal Investigators to observe the fields and record if they found evidence of stressors. These observations were not standardized, but led to the development of the methods used in 2011 (please see response to 6b below).

b. Page 134 of the main application states: "In 2011, a more rigorous method to evaluate insect, disease, and abiotic stressors was implemented using a rating scale to compare plant damage or response to the selected stressors. Data recorded reflected the presence or absence of the stressor as well as severity. Ratings were considered different if the ranges did not overlap". Page 37 of Appendix 6 clarifies that individual observations for each stressor were totaled across time points and sites. However, the methodology remains unclear on a number of points. Please provide more information on how these observations were made. Were the observations made at every study site? How many observations were recorded for each stressor during the season? Were all plants thoroughly examined for each stressor or were a number of plants randomly selected? Were any stressors observed that were not noted in the analysis? Please include any other relevant details.

Response: In 2011, methods for collecting such data were significantly improved, and those results are summarized in Table 22. We included all the data from 2009, 2010, and 2011 in the submission, although we recommend that more emphasis be placed on results from 2011. In 2011, the observations were made at every study site. All plants in a plot were looked at for stressors or evidence of stressors. Principal Investigators were instructed to choose three insect stressors, three disease stressors, and three abiotic stressors to evaluate during each observation. The stressors were not predetermined and were selected independently for each growing environment based on the presence of stressors and the

site history. There were three stressor observations conducted over the course of the growing season. It was not required that the same stressors be evaluated during each observation. The choice of stressors was also based on crop stage. Therefore, there is no set number of observations for each stressor. We have presented the total number of observations for each and the numbers are variable by design.

c. Please expand upon the rating scale used in this study. For example, please provide the description for each step in the scale.

Response: The rating scales are explained in the updated footnotes of updated Table 15 as shown in our response to question 2 above.

d. The total number of stressor observations in 2011 ranged from 3 to 18 observations per stressor for events F10 and E12 and from 3 to 65 observations per stressor for events J3 and J55. Please provide a scientific justification that this number of observations is sufficient to determine that the events do not have any increased potential to harbor new or increased populations of pathogens or pests.

Response: Please see response to 6b above for an explanation of the methods and why the number of observations were variable. These data were observational, qualitative, and not statistically analyzed therefore power analysis of the sample size was not possible. In a total of 11 field trials for the Ranger Russet F10 and Russet Burbank E12, and 15 field trials for Atlantic events J3 and J55, with at least three replicates per trial, all provide supporting evidence that the events respond similarly to controls.

7. No information was given on the relative abundance of any non-pest species associated with field-grown potatoes (e.g. beneficial organisms such as pollinators or mychorrhizal fungi). Please provide this data, if available, and discuss how it supports the position that the four events are not expected to adversely affect this important group of organisms. Please discuss this in terms of the potential for the events to impact biodiversity or harbour new or increased populations of pests.

Response: Potato fields harbor various mammalian, avian, reptilian, arthropod and microbial species. Beneficial insects such as Orius species, Nabid species, Coccinelids, and parasitic wasps are important for integrated pest management and are prevalent in both Canadian and U.S. production regions.
The inserted DNA acts by silencing enzymes targeted at quality traits, and these changes are not expected to affect other organisms in potato fields, either pests or non-pests. The mechanism of RNAi silencing is highly specific to reduction of targeted enzymes and the phenotypic, agronomic and composition studies support the hypothesis that no other characteristics were changed. As such, these events are not expected to impact on biodiversity in the growing environment any more than conventional potatoes. For additional information on RNAi silencing, please see our response to question 11 below.

8. The compositional assessment described in Section 9 of the main application and Appendix 9 indicates there is a reduction of the amino acid asparagine and an increase in free glutamine and total glutamine + glutamic acid in the tubers of all four events. Please discuss the potential effects of these changes in amino acids on NTOs.

Response: All free amino acids remain in abundance and within the normal range for potatoes. As such, this change is not expected to affect any non-target organisms.

9. Section 8.2 of the main application and Appendix 8 describe studies aimed to determine differences in susceptibility to late blight and bacterial soft rot between the four events and their controls. Section 7 of the main application and Appendix 6 also compare stressor observations between the events and their controls for four pest insect species and seven diseases. Other major pathogens in Canada include those that cause pink rot, Fusarium dry rot, Phythium leak, silver scurf, common scab, aerial stem rot and bacterial soft rot. Other major insect pests in Canada include tarnished plant bug, potato leaf hopper, potato flea beetle, European corn borer, wireworms, and flea beetle. Please describe how the data presented in the application relates to the relative susceptibility between the events and conventional potatoes for the insects and diseases found in Canada, including those listed above.

Response: Please see Supplement A for a discussion of the applicability of U.S. field trial locations. The document contains a section on major pests and high-level control practices and concludes that insect and disease pressure and control are similar between regions. The decreased expression of targeted quality traits is not expected to impact on pest abundance or susceptibility to Canadian fungal and insect pests (see response to Question 10, below) and this hypothesis was supported by the U.S. field evaluations. The existing pest management tools available to Canadian farmers will remain applicable to production of these potato events.

10. Page 141 of the main application states: "A number of researchers evaluated induced PPO activity and response mechanisms to biotic stressors, in particular pests and pathogens (Steffens et al. 1994)" and "Studies with biotech tomatoes found a positive correlation between high levels of PPO in leaf tissue and increased resistance to pathogens and insect pests (Li and Steffens 2002)". Similarly, page 2 of Appendix 8 states "Researchers have investigated the relationship between PPO and disease resistance (Valentines et al. 2005; Li and Steffens 2002; Hakimi et al. 2006); with some proposing that enhanced PPO may increase resistance to disease, while others claim that reduced PPO could increase resistance." Please provide a more robust discussion of the scientific literature as it pertains to the role of polyphenol oxidase in plant disease and insect susceptibility. Please link this discussion to the possibility of altered plant pest potential of potato events E12, F10, J3 and J55 and the results obtained in both Appendix 6 and Appendix 8.

References:

**Hakimi S.M., Krohn B.M., Stark D.M. 2006. Monsanto Technology LLC United States Patent: Method of imparting disease resistance to plants by reducing polyphenol oxidase activities.
Patent No.: US 7,122,719 B2.**

Li, L. and Steffens, J.C. 2002. Overexpression of polyphenol oxidase in transgenic tomato plants results in enhanced bacterial disease resistance. Planta 215: 239-247.

Steffens, J.C., Harel, E. and Hunt, M.D. 1994. Polyphenol Oxidase. In: Genetic Engineering of Plant Secondary Metabolism (Ed. B.E. Ellis). Plenum Press, New York, pp. 275-312.

Valentines M.C., Vilaplana R., Torres R., Usall J. and Larrigaudiere C. 2005. Specific roles of enzymatic browning and lignifications in apple disease resistance. Postharvest Biotech and Tech, 36: 227-234.

Response: To address this question, we are providing an updated version of Chapter 8 (please see Supplement C). In addition, we are submitting a revised Section 12.3 (Potential to Become a Plant Pest) below with a more complete discussion of the Environmental Safety Assessment.

12.3 Potential to Become a Plant Pest (Revised)

Information in this submission related to plant pest risk characteristics of events F10, E12, J3, and J55 include: 1) mode-of-action; 2) composition; 3) potential for weediness; 4) impacts to non-target organisms (NTOs); 5) disease and pest susceptibilities; 6) impacts on agronomic practices; and 7) impacts on the weediness of any other plant with which it can interbreed, as well as the potential for gene flow.

The modifications to events F10, E12, J3, and J55 all result from gene silencing, which acts to reduce expression of the *Asn1* and *Ppo5* genes, resulting in lower free asparagine and polyphenol oxidase in potato tubers. In addition, the promoters for *R1* and *Phl* were silenced to affect the level of reducing sugars, however the promoter silencing was only partially effective in altering sugar levels. The mode of action for down regulation of the targeted genes and does not include or result in pesticide or herbicide activity. Compositional data for events F10, E12, J3, and J55 are within the normal range for potatoes indicating that there has been no major nutrient changes associated with the gene silencing mechanism. All of these observations provide evidence that the gene silencing has not influenced the plant pest potential of the potato events.

Data collected and reported in the Agronomic Performance section show that over multi-year and multi-site field trials no variety specific differences leading to increased weed or pest potential were present. Weediness and invasiveness are already considered in this section and the data on abiotic and biotic stressors included in the Agronomic Performance section indicate that there are no noticeable differences in susceptibility to pests and diseases common to potatoes in Canada. The traits associated with these events are not pesticides and as such have neither target organisms nor non-target organisms that could be negatively impacted. . The novel traits introduced into the events do not function to alter disease susceptibility and specific testing for certain diseases together with field observations for a wide range of pests and diseases, has confirmed this. These studies with late blight and bacterial soft rot confirmed that silencing of the target genes did not enhance susceptibility to these common diseases. As expected, these traits were not designed to affect agronomic practices and multi-year field trials support the conclusion that no changes in agronomic practice would be required.

Based on these results, we conclude that silencing of *Asn1, Ppo5* or the promoters associated with *R1* or *Phl,* does not consistently influence disease susceptibility. However, if any events showed slightly higher susceptibility to disease, it would not enhance their weediness or result in the creation of plant pests.

The silencing strategy, using AGP and GBSS promoters, deliberately targeted silencing in tubers and not the whole plant. Along with targeting the tuber specific *Ppo5* gene, this suggests that events F10, E12, J3, and J55 are expected to be unchanged relative to PPO gene expression and PPO levels in leaves and therefore unchanged in any potential interactions between potato foliar PPO and foliar pathogens or pests. The RNA expression studies described in Section 6.1, Tissue Expression Studies (Table 12) of the original submissions, provide additional evidence that PPO silencing was most effective in tubers, and largely ineffective in leaves.

No consistent differences were observed in foliar pest and pathogens on events F10, E12, J3, and J55 compared to their control varieties.

In conclusion, the agronomic performance studies showed no biologically meaningful differences that would contribute to increased pest potential. There is no indication of a potential for these four potato events to become either a plant pest or to increase the level of known pests and diseases of potato in Canada. In the unlikely event that increased plant pest levels are observed, existing pest management measures and practices will be implemented to prevent increased plant pest potential in Canadian production systems.

11. Please provide a robust scientific justification as to why the RNAi technology used to produce the novel traits expressed in the four events would or would not be expected to have any potential impacts on NTOs. Please cover, but do not limit the discussion to, the following topics:

(i) why the dsRNA/siRNA produced by the four events would be likely or unlikely to interact within the body of any NTOs with respect to physical and physiological barriers;

(ii) the possibility that that the genetic elements responsible for gene silencing in the four potato events could or could not contribute to gene silencing in NTOs, including humans;

(iii) the presence/absence of the down-regulated processes outside of the plant kingdom;

(iv) the relative expression levels of the dsRNA/siRNA within the various tissues in the four events;

(v) the expected degradation time of the dsRNA/siRNA in the environment after the potato crop is removed (i.e. from small potato tubers and other plant material left in the soil); and

(vi) any shared sequence homology between any unexpected putative polypeptides produced by the insert and known toxins, allergens, or biologically active putative peptides. Your response should include a discussion of Zhang et al. (2102), Wang et al. (2012), Lukasik and Zielenkiewicz (2014), and other relevant papers.

References:

Zhang, L., Hou, D., Chen, X., Li, D., Zhu, L., Zhang, Y., Li, J., Bian, Z., Liang, X., Cai, X., Yin, Y., Wang, C., Zhang, T., Zhu, D., Zhang, D., Xu, J., Chen, Q., Ba, Y., Liu, J., Wang, Q., Chen, J., Wang, J., Wang, M., Zhang, Q., Zhang, J., Zen, Ke, Zhang, C-Y. 2012. Exogenous plant MIR168a specifically targets mammalian LDLRAP1: evidence of cross-kingdom regulation by microRNA. Cell Research 22: 107-126.

Wang, K., Li, H., Yuan, Y., Etheridge, A., Zhou, Y., Huang, D., Wilmes, P. and Galas, D. 2012. The complex exogenous RNA spectra in human plasma: an interface with human gut biota? PLoS One 7: DOI: 10.1371/journal.pone.0051009.

Lukasik, A. and Zielenkiewicz, P. 2014. *In silico* identification of plant miRNAs in mammalian breast milk exosomes – a small step forward? PLoS One DOI: 10.1371/journal.pone.0099963.

Response: These topics are addressed in three supplements included in the CFIA/Health Canada questions from August 27, 2014. The supplements are included in this response as follows.
Supplement D: Analysis of pSIM1278 siRNA Targets and Specificity
Supplement E: Safety Considerations for Nucleic Acid, including Double-Stranded RNA and siRNA
Supplement F: Bioinformatics Analysis of Insert

Supplement A

Agronomic Practices: Comparison between U.S. and Canada

Report by The Context Network, written for Simplot Plant Sciences

October 7, 2014

Executive Summary

In order to further the work of Simplot's recent agronomic trials evaluating the potential agronomic performance of the Russet Burbank Event W8, The Context Network (Context) has provided this document comparing the various U.S. field trial locations with Canadian potato production regions. The purpose of this document is to clearly identify the Canadian regions which share the highest degree of commonality with Simplot field trial locations. The second purpose of this document is to compare the similarities of these regions based on various factors, such as: potato varieties grown, soil types, pests, fertility practices, agronomic practices, and climate conditions.

Context found that many of the U.S. field trial locations share similarities with multiple regions throughout Canada. However, each field location was paired with the Canadian region to which it was most similar. These pairs of regions and field locations tended to line up based on elevation, climate, and similar potato production zones. The following table summarizes the pairs we identified:

U.S. Field Trial Location	Canadian Potato Production Region
Centre County, PA	New Brunswick
Ionia County and Montcalm County, MI; and Adams County, WI	Quebec
Ionia County and Montcalm County, MI; and Adams County, WI	Ontario
Sherburne, MN and Grand Forks, ND	Manitoba
Canyon and Jerome County, ID	Saskatchewan
Minidoka and Jerome County, ID	Alberta
Grant and Adams County, WA share many similarities with Canyon County, ID	

Project Overview

Simplot has recently completed trials that were used to evaluate the potential agronomic performance of Russet Burbank Event W8 in Canadian agriculture by using similar environments within U.S. growing regions. The performance of Event W8 was compared to a Russet Burbank Control to evaluate performance and environmental impact. The key objective of these studies was to generate data from field trials using sites in the United States that were relevant to Canadian growing conditions. Multiple reports support the assumption of similar growing conditions between the Northern U.S. and Canada with similarities in the following areas:

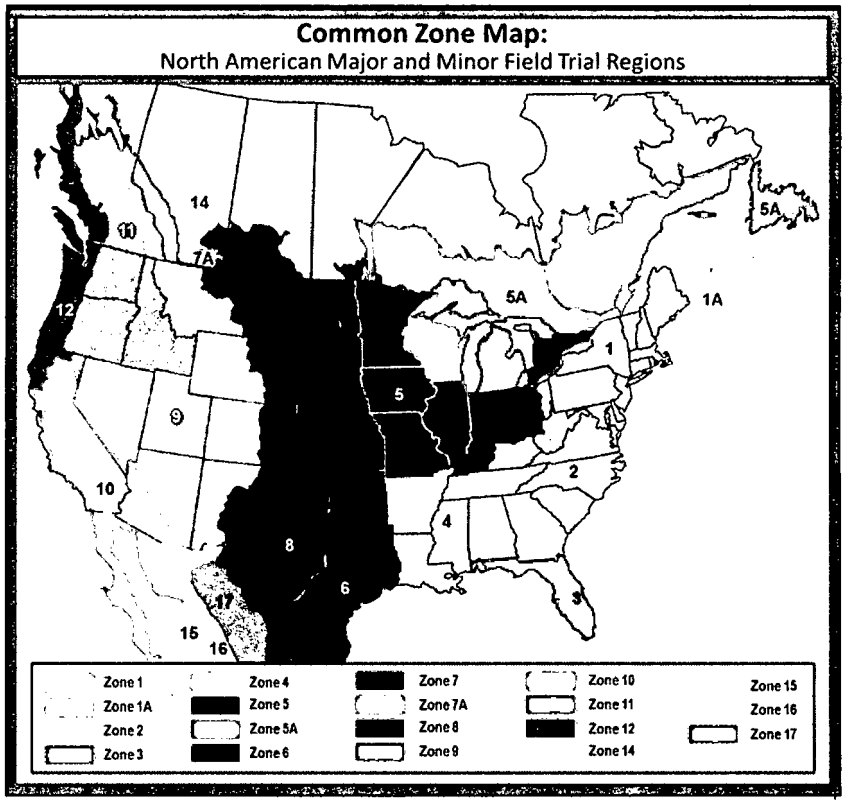
- Potato varieties grown
- Insect and disease pressure as well as control methods
- Abiotic stressors
- Potato yields

In conducting the field trials, Simplot observed the plants throughout the growing season, allowing for a thorough assessment of (1) growth, (2) disease and pest susceptibility, and (3) tuber yield and quality. It was confirmed through this assessment that the W8 event has the intentionally-incorporated new traits while still maintaining the positive characteristics of the conventional Russet Burbank. The field trials also calmed fears relating to unintended effects of the trait. Simplot has provided this information to Context. In this report Context will identify regions in Canada that closely match the sites used in the U.S. field trials. These identified Canadian regions will then be compared to the U.S. field trial sites in terms of the following physical characteristics and grower practices:

- Potato varieties grown
- Basic soil types
- Major pests (weeds, diseases, and insects) and high-level control practices
- General fertility practices
- Overall agronomic practices (tillage, rotations, harvest, etc.)
- Rainfall, temperature, and general weather patterns

Background

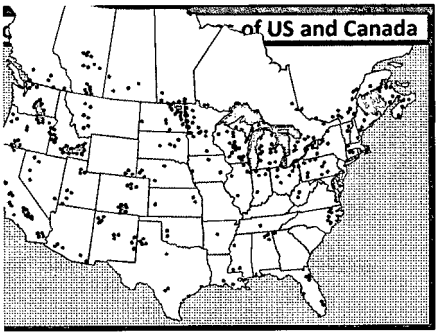
The relationship between U.S. and Canadian growing regions allows for the consideration and acceptance by one country of data from field trials conducted in the neighboring country. This precedence was set by the U.S. Environmental Protection Agency (EPA); the EPA will consider Canadian field trial results for U.S. registration. Canada has returned the same consideration for U.S. field trials, which allows the Canadian registration of new pesticides and other products based on technical results generated in the U.S. This Canadian consideration of data, studies, and conclusions based



upon supervised field studies conducted within the U.S. which are deemed indigenously equivalent by Health Canada is available through the Office of Pest Management Regulatory Agency (PMRA).

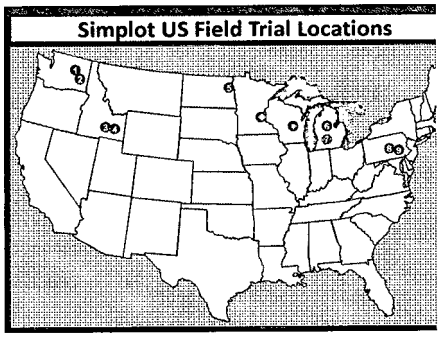
As a result of this arrangement, scientific field studies conducted under good laboratory practices are accepted as relevant to regulatory decisions if the experiments reside within areas that represent the agro-climatic zone where agronomic management and growing seasons are similar. The *Common Zone Map* illustrates the agro-climatic zones that are common between the U.S. and Canada (Source: Crop Profile for Potato in Canada, 2011).

As seen from the *Common Zone Map* there are seven zones in common between the Northern U.S. and Canada. These seven zones from East to West are: 1, 5A, 5, 7, 9, 11, and 12. The common zones are similar in many edaphic and climatic features and are used by the U.S. EPA and the Canadian PRMA. The regions are defined by a number of common parameters, including similar soil types and seasonal climate according to the PMRA Regulatory Directive 2010-05 Revisions.



In Canada overall, soil conditions best suited to potato production are deep, well-drained, sandy loam or silt loam soils. These characteristics of Canada's potato production areas are in alignment with those of the United States, where the similar soil types and climates boast high yield potential across the commercial potato production regions in the Northern U.S. Due to the similarities in soil and climate along the Canadian – U.S. border, potato production has been concentrated in these clusters of similar production areas. The map titled *Potato Production Areas of the United States and Canada* illustrates these production clusters (Source: Potato Health Management, APS, 1993).

As illustrated and described above in regards to common growing zones and clusters of potato production, there are many similarities between Canada and the U.S. in terms of potato production. The zones identified in common between the two areas align with the Simplot field trial locations which are depicted in the graph titled, *Simplot US Field Trial Locations*. The remainder of this report will identify the common zones which exist between the U.S. and Canada and then proceed to discuss the similarities.



Identification of Common Growing Regions

Multiple growing regions exist between the U.S. and Canada that have various levels of commonality. This section will identify those regions in Canada which are most in common with the field trial locations from the Simplot trials in 2012 and 2013. Initially it is important to describe and define the U.S. Field Trial Locations. *Table 1: Major Characteristics of Field Location Sites* (located in the Appendix) describes the characteristics of the U.S. field trial locations.

A key take-away from the comparison of the field location sites is the already-existing similarities in the agronomic practices between locations in the Northern U.S. Comparing these similarities leads to the following understanding about potato production areas:

- Soil types in potato production areas are most commonly sandy and/or silty loams.
- Pest pressure comes from similar sources such as Aphids, Lambsquarters (weed), and Late Blight.
- Control practices are similar in applying pre-plant fumigants, seed treatments, and foliar fungicides after row closure to manage fungus growth from increased humidity under the canopy.
- Standard tillage practices and center pivot irrigation are used on the majority of potato production.

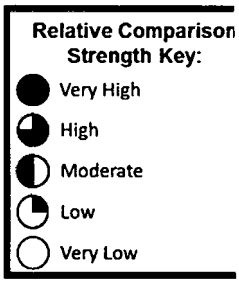
Two areas where there are differences between the growing regions are climate and fertility practices. This is logical because fertility practices are closely tied to the climate of the growing region. For example, in the Columbia Basin of Washington, a longer growing season results in a higher use of NPK compared to other regions, whereas in Michigan a wetter and more temperate climate creates the need for slow-release and starter fertilizers which provide nutrient to the plant even after row closure (in Michigan, the growers will not fertilize after row closure).

The following regions in the U.S. and Canada were identified as being similar to one another. Elevation, growing zone, production clusters/continuous production, and climate were the most influential factors in determining the regions which share the most commonalities. Elevation is a strong reflector of the length of growing season and helps separate shorter growing seasons, which will lean more towards seed production, from the longer growing season areas, which focus on commercial production. The following table identifies the U.S. field trial locations with the Canadian provinces they resemble, along with the rationale behind the comparison.

Common Growing Regions between the United States and Canada		
Canada	United States	Rationale
Prince Edward Island	N/A (Maine shares commonalities with PEI)	• Centre County, PA may have some similarities in climate and the two regions share a zone
New Brunswick	Centre County, PA	• Similar elevations with PA at 1,400 ft. and NB ranging from sea level to around 1,000 ft. • Same zone
Quebec	Ionia County and Montcalm County, MI; and Adams County, WI	• Similar elevations around 1;000 to 1,500 ft. • Same zone
Ontario	Ionia County and Montcalm County, MI; and Adams County, WI	• MI/WI has slightly lower elevation at 1,000 ft. and Ontario has an elevation of 1,000 to 2,100 ft. • Same zone • Production is continuous from WI/MI to Ontario
Manitoba	Sherburne, MN and Grand Forks, ND	• 1,000 ft. elevation in the US and growing to 2,100 ft. in MAN, same climate zone, production cluster in ND/MN and Manitoba
Saskatchewan	Canyon and Jerome County, ID	• Moderate elevations at 2,000 to 3,000 ft. • Same zone • Isolated production regions
Alberta	Minidoka and Jerome County, ID	• Higher elevations at 4,000 ft. • Same zone • Isolated production regions • Colder/shorter growing season
British Columbia	N/A	• Low elevation climate • Same zone as Grant and Adams County, WA but BC is a temperate, high moisture region where Grant and Adams County are hot and dry with the longest growing season
Grant and Adams County, WA share many similarities with Canyon County, ID		

As Context compared the U.S. field trial location characteristics with the potato producing regions of Canada it became apparent that certain agronomic practices are synonymous with potato producing regions. For example, the soils described in both the field trial locations and the Canadian regions are sandy/silty loams which result in light, well-draining soil. In order to identify the similar regions, Context characterized the defining and unique characteristics of the regions and compared the similarities. After the similar regions were identified, Context conducted a regional comparison by evaluating the specific physical characteristics and agronomic practices of each region.

Context compared the pairs of regions that rate the highest in terms of similarities. Factors that were compared include: soil type, pest pressure, agronomic practices, climate zone, rainfall, elevation, production cluster, yield, and end-use focus. Each regional pair was given a score based on these factors. A propeller chart score card was used to rate these characteristics, demonstrated in the chart on the right.



Centre County, Pennsylvania and New Brunswick, Canada

The first comparison conducted was of Centre County, Pennsylvania and New Brunswick, Canada. This region has an overall assessment of *HIGH*. The factors of greatest similarity were climate zone, rainfall, and yield. A key note is that elevation is similar but much of NB production is between sea level and 800 feet where production in Pennsylvania is at an elevation of 1,400 ft. or higher. These areas differ in terms of pest pressure.

Comparison of Centre County, Pennsylvania to New Brunswick, Canada

	Center County, PA	New Brunswick, Canada	Similarity Rating	Comments
Soil	Gravelly sandy loam	Fine sandy loam	◕	Sandy soils like most potato production regions
Pest Pressure			◐	PA faces more pest pressure from CO Potato Beetle and Late Blight
Agronomic Practices			◐	Similar practices for fertility, irrigation, etc. (lower irrigation use in NB)
Climate Zone	1	1	●	
Rainfall (in.)	39	39	●	
Elevation (ft.)	1,400	0-800	◔	
Production Cluster			◕	Both in Northeast region of North America
Yield (cwt./acre)	260	265	●	
End-Use Focus	Chips	Dehydrated and Frozen	◐	NB: CANUSA Foods, Asapco, McCain
Overall Assessment			◕	

Michigan/Wisconsin and Ontario, Canada

A comparison between the Michigan/Wisconsin growing regions and Ontario, Canada was also of interest. The most similar categories were soil (both sandy loams), climate zone, and elevation. The regions differ in terms of production clusters, end-use focus, and yield. The yield is likely to differ so significantly because of micro-climates that are created around the Great Lakes Region. Rainfall in this growing region can easily fluctuate 10 inches above average during the growing season (Kirk, W.W., Michigan State University). These regions are *HIGHLY* similar in their practices.

Comparison of Michigan and Wisconsin Growing Regions to Ontario, Canada

	Michigan & Wisconsin	Ontario, Canada	Similarity Rating	Comments
Soil	Sandy Loam/Loam	Sandy Loam	●	Sandy soils like most potato production regions
Pest Pressure			◕	Similar pressure from late blight and aphids. MI/WI has more pressure from CPB
Agronomic Practices			◕	Similar irrigation practices
Climate Zone	5A	5A	●	
Rainfall (in.)	33 (average 15 growing season)	27	◕	
Elevation (ft.)	700-1,100	1,000 – 2,100	●	
Production Cluster			◐	North Central North America
Yield (cwt./acre)	350-450	190	◐	
End-Use Focus	Chips & new potatoes	Frozen	◐	
Overall Assessment			◕	

Minnesota/North Dakota and Manitoba, Canada

The Minnesota/North Dakota region and the Manitoba, Canada region are the most similar overall in comparison to all other regional pairs. Minnesota and North Dakota are part of the same dense production cluster as Manitoba. Other factors of similarity include pest pressure, agronomic practices, climate zone, elevation, production cluster, and end-use focus. The extreme similarity is logical because of the continuous nature of this production region. The differences in yield and rainfall are the most disparate. This rating is *EXTREMELY HIGH*.

Comparison of Minnesota and North Dakota Growing Regions to Manitoba, Canada				
	Minnesota & North Dakota	Manitoba, Canada	Similarity Rating	Comments
Soil	Fine sand / silt clay loams	Sandy to clay loam	●	Sandy soils like most potato production regions
Pest Pressure			◕	Moderate pressure from late blight. MN/WI has more pressure from aphids.
Agronomic Practices			◕	Irrigation is key for these areas
Climate Zone	5	5	●	
Rainfall (in.)	30	20	◐	
Elevation (ft.)	900	1,000 – 2,100	●	
Production Cluster			●	
Yield (cwt./acre)	300-400	275	◐	
End-Use Focus	Processing	Processing	●	McCain, Cavendish, and Simplot are in this region
Overall Assessment			●	

Idaho and Alberta, Canada

The Idaho growing region and Alberta, Canada are also *HIGHLY* similar in the overall assessment. In regards to end-use products these regions are the most similar of any regional pair as they both focus on French fries, and neighboring areas to the Manitoba and Idaho production regions also focus on seed. With their higher elevations comes colder climates and more remote areas, perfect for seed production. Additionally, with lower rainfall all of the acres

Comparison of the Idaho Growing Region to Alberta, Canada				
	Idaho	Alberta, Canada	Similarity Rating	Comments
Soil	Silt loams	Sandy to silt loams	●	Sandy soils like most potato production regions
Pest Pressure			◐	Similar concern for aphids and late blight and Potato Virus M-R (seed potato focus)
Agronomic Practices			●	Irrigation causes the higher yields
Climate Zone	11	14	◔	Neighboring zones and both offer colder, higher elevation, remote climates
Rainfall (in.)	10	15	◕	
Elevation (ft.)	3,700-4,200	4,600-5,300	●	
Production Cluster			◐	
Yield (cwt./acre)	410	344	◕	
End-Use Focus	Fries	Seed & Fries	●	Remote and cold region is ideal seed climate
Overall Assessment			◕	

are irrigated, creating higher and more similar yields. The factor with the least similarity is climatic zone with the 2 regions only classified as neighboring. However, these production areas are rated as *HIGHLY* similar in regards to their grower practices.

Regional Comparison

The regional comparison will focus on identifying the grower practices which are similar between the Canadian and U.S. growing regions. The comparison will focus on potato varieties, basic soil types, major pests and high-level control practices, general fertility practices, overall agronomic practices, and growing climate. The intent of the regional comparison is to draw similarities between the locations based on these characteristics to allow for reasonable grounds in demonstrating the similarity of the agro-climatic zones that will justify acceptance of the field studies conducted in the U.S. by Health Canada.

Potato Varieties

Many of the important cultivars grown traditionally in Canada are likewise grown in the U.S. primarily because they are well-adapted to a large geographic area and meet end-user expectations (ERS, 2011). The following table, *Important and Familiar Potato Cultivars Grown in the United States and Canada*, reflects the varieties which are similar between the two regions (Source: 2011 Canadian Crop Profile, 2011 ID PLB Action Plan, and Potato Health Management, APS, 1993).

Important and Familiar Potato Cultivars Grown in the United States and Canada			
Cultivar	Year of Release	Agency	Strength/End Uses
Russet Burbank	1914	Private	Wide market use, good storability
Kenebec	1948	USDA – Maine	Chips
Superior	1961	Wisconsin	Excellent type, Fresh Market
Atlantic	1976	USDA – Beltsville	Fresh Market, Chips
Shepody	1980	Ag Can, NB	Processing Quality, French Fries
Russet Norkotah	1987	North Dakota	Fresh Market
Ranger Russet	1991	USDA and ag stations of ID, WA, OR, and CO	High specific gravity and late-maturing potato, baking and processing into fries
Snowden	1990 (unofficial release)	University of Wisconsin	Potato Chip Market

Other varieties in common between the U.S. and Canada include Umatilla Russet for French fries and Yukon Gold for fresh market table stock.

History demonstrates that research results on breeding and selecting, as well as cultivar responses to factors such as crop rotation, fungicides, and fertilizer are largely applicable within

and across regions. The historical data supports the acceptance of the Russet Burbank Event W8 by Health Canada because the field trials conducted in 2012 and 2013 are similar to other field trial results previously adopted.

USDA and U.S. university research has previously obtained results and progress on genetic gains for other cultivars and varieties in terms of yield, quality, and disease resistance. The generated data has led to the successful adoption and market merit in Canada. Likewise, the reciprocal value of Ag Canada efforts in potato crop improvement have been recognized by the U.S. National Potato Council.

Basic Soil Types

As mentioned previously, soil conditions in the both the U.S. and Canada are highly similar with the major potato production regions possessing the soil type best suited for potato production. Common potato production soils in both Canada and the U.S. are deep, well-drained, sandy loams or silt loam soils (Crop Profile for Potato in Canada, 2011, 2005). These soil conditions will boost yields, especially in areas where irrigation is practiced (APS, 1993 and Potato IPM UC, 1986).

The tables below show the soil types in both the selected counties in the United States and the provinces in Canada. The soil type classification is based on soil samples in potato production areas in these regions (USDA, Natural Conservation Resource Service – Interactive Soil Surveys).

U.S. Growing Regions		
State	County	Soil Types
WA	Grant	Fine sand and silt loams
WA	Adams	Fine sandy loams to silt loams
ID	Jerome	Silt loams, gravelly loams
ID	Canyon	Silt loams
ID	Minidoka	Silt loams
MN	Sherburne	Fine sand
ND	Grand Forks	Silt clay loams, loams
WI	Adams	LoamysSand, sand
MI	Ionia	Loams
MI	Montcalm	Sands and sandy loams
PA	Centre	Gravelly sandy loams

Canada Growing Regions	
Province	Soil Types
PEI	Fine sandy loam
NB	Fine sandy loam
QUE	Sandy loams
ONT	Sandy loams in the Southwest
MAN	Sandy to clay loam soils
SAS	Sandy loam
ALB	Sandy to silt loam
BC	Gravelly sandy loams

As seen in the above tables, the potato production areas are typically a sandy/silty loam soil classification. An additional comparison here can be drawn between the Centre Country, Pennsylvania field location and British Columbia; both regions have gravelly sandy loam soils.

Major Pests and High-Level Control Practices

U.S. and Canadian potato production areas face similar pressure from diseases, insects, and weeds. In Canada, Potato Late Blight has been mentioned as the highest-pressure disease in PEI, Ontario, Alberta, and British Columbia, with moderate pressure reported in Manitoba, Quebec, and Saskatchewan.

In the U.S., the Great Lakes region reports the highest disease pressure from Late Blight. The Michigan and Wisconsin field trial sites are most similar to the Ontario and Quebec provinces where high and moderate disease incidence exists, respectively. Dryer areas, like the Columbia Basin of Washington, are concerned about Late Blight but have been able to manage the disease. The majority of control practices in regards to the disease pressure are related to sanitation and proper handling of potato seeds and equipment. The following table illustrates the disease pressure, by Late Blight and other diseases, faced in North America.

Additional pest pressure comes from insect pests, with the most concerning being Aphids and

Disease Incidence and Severity in North American Production									
	PEI	NB	QUE	ONT	MAN	SAS	ALB	BC	USA
Potato Late Blight	H	L	M	H	M	M	H	H	Y*
Early Blight	L	L	L	M	H	H	L	L	Y*
Verticillium Blight	L	M	VL	H	L	M	L	H	Y*
Potato Leaf Roll Virus	M	VL	L	M	L	L	L	M	Y*
Potato Virus M-R	M	L	M	M	H	M	H	H	Y*

[redacted]

Colorado Potato Beetle. Again, the Michigan growing regions face similar insect pressure to Ontario and Quebec, with highest pressure coming from Aphids, Colorado Potato Beetle, and Leafhoppers. The Alberta and Saskatchewan growing regions face lower insect pressure because of their higher elevation, colder temperatures, remote areas, and dryer regions. The insect pressure is managed through the use of insecticides.

The Pacific Northwest potato growing regions, Washington and Idaho, have experienced a similar phenomenon with one expert citing their ability to manage insects like Colorado Potato Beetle through the use of Neonicotinoids. These pesticides have controlled previously primary pests and reduced them to secondary concerns. The following table addresses the severity of insect pressure in North America (please refer to Table 1 in the appendix for further detail on U.S. growing sites. Refer to the disease table above for abbreviation definitions).

Occurrence of Insect Pests of Potato in Canada and United States									
	PEI	NB	QUE	ONT	MAN	SAS	ALB	BC	USA
Aphids	H	L	M	M	L	M	H	M	Y*
Colorado Potato Beetle	L	L	L	VL	H	H	H	M	Y*
Leafhoppers	M	L	L	L	H	M	L	L	Y*
Wireworms	H	L	H	M	M	L	L	M	Y*
Flea Beetle	H	L	L	VI	L	M	M	M	Y*

The final pest category of concern are the weeds that are a challenge to potato production. Weeds can lower yields due to competition and serve as hosts for insects and diseases. The highest weed pressure comes from annual broadleaves, like Russian thistle, in both the U.S. and Canada. Weed pressure is managed through herbicides registered for both the U.S. and Canada. These herbicides are commonly used in potato production: paraquat or glyphosphate (applied before planting), metolachlor, meribuzin, sethoxydim, fimsulfuron, and clethodim. The following table describes the weeds that are common throughout all potato production regions in both the U.S. and Canada (please refer to Table 1 in the appendix for further detail on U.S. growing sites. Refer to the disease table above for abbreviation definitions).

Problematic Weeds Common to Potato Production in Canada and the United States									
	PEI	NB	QUE	ONT	MAN	SAS	ALB	BC	USA
Annual Broad Leaves[1]	L	M	H	VI	H	H	VI	L	Y*
Annual Grasses[2]	L	M	M	VL	M	M	VL	L	Y*
Perennial Broadleaves[3]	L	M	H	VL	H	H	VL	M	Y*
Perennial Grasses	L	M	L	VI	H	H	VI	M	Y*
Solanaceous Weeds[4]	L	M	VL	VL	M	M	VL	VL	Y*

An additional pest that needs to be mentioned is mold, which becomes a challenge upon row closure in potato production areas. This challenge is managed through fungicide applications after row closure and is faced in all of the major potato growing regions.

Beneficial Insects

Beneficial insects enhance control of many potato pests. These beneficial insects include: Orius species, Nabid species, Coccinelids, and parasitic wasps. These insects are prevalent in both Canadian and U.S. production regions. The following chart describes the characteristics of these insects. All of these insects are available commercially to be used in production regions.

Beneficial Insects			
	Examples / Common Name	Prey Attacked	Dominant Growing Regions
Orius	Minute Pirate Bugs	• Insect eggs and other soft-bodied insects • Potato Leafhoppers	Common near spring and summer flowering shrubs and weeds.
Nabid	Example) Damsel Bug	• Insect eggs, aphids, and small caterpillers • Potato Leafhoppers	All production regions
Coccinelids	Lady Bugs	• Aphids and other small insects • Lady Beetles can feed on CO Potato beetle	All production regions
Chrysoperla	Common Green Lace Wing	• Specializes in aphids	Better for row crops in drier areas
Parasitic Wasps		• Aphids • Colorado Potato Beetle	All production regions

General Fertility Practices

Fertility practices differ across all growing regions because of both cultural and climatic differences. However, certain similarities exist between the growing regions specifically tied to the soil, rainfall, elevation, growing season etc. Suggested fertilizer rates for potato production are broadly based on the type of soil, prior crop, soil texture, residues present, and other factors. Soil samples provide the most accurate assessment of nutrient needs.

Context has summarized the general nutrient requirements of potato crops in varying regions in the following table. Requirements were approximated based on similar patterns of nutrient consumption, uptake, and utilization seen in the U.S. and Canada.

Estimated Nutrient Requirements of Selected Regions in North America							
Region	Nitrogen (lb/Acre)	Soil Phosphorus Results (lbs/Acre)			Soil Potassium Results (lbs/Acre)		
		Very Low	Low	Medium	Very Low	Low	Medium
New England	120-180	300	250	200	250	225	180
Mid Atlantic	125-150	200	100	50	200	100	0
Manitoba	78-80	40-45			100-150		
Ontario	160-170	50-55			220-230		

General fertility practices throughout the potato production regions in the Northern U.S. and Southern Canadian areas vary. The fertility practices reflect the nutrient requirements of the soil, the climate, and also some cultural influences. For example, growers in the Michigan growing areas do not fertigate their crop and must fertilize before canopy closure, thus pushing their region towards slow-release and starter fertilizers.

In the Columbia Basin, fertility practices reflect the longer growing season for potatoes and result in a higher use of fertilizer to meet the demands of more growing days. Producers in this dryer, hotter climate, with 30-50 more days in a growing season compared to other U.S. and Canadian production regions, must apply fertilizer for this extra growing time.

Overall Agronomic Practices

Agronomic practices are consistent across the U.S. and Canada with the large majority (99% +) of production area irrigated. Irrigation is most often supplied through center pivots. A 2-4 year rotation is common in almost all regions. Crop rotation in the Michigan, Wisconsin, Minnesota, and North Dakota regions includes wheat, corn, and soybeans, which is similar to that of nearby Canadian growing regions. The Western U.S. rotates with wheat and corn. Harvest is usually from late July through late October with the Columbia Basin of Washington starting earliest towards the beginning of July.

Growing Climate

Climate is most accurately reflected in the Common Zone maps, showing areas of similar climate. In comparing the growing climate of different regions, Context analysts collected data on various elevation differences across the growing regions and the results are presented in the table, *Elevation of North American Growing Regions.*

A strong reflector of growing season length is elevation, and this factor was used to help draw similarities between U.S. and Canadian growing regions. Other climatic factors that were of interest to Context were rainfall and temperature. The higher rainfall areas are in the Eastern growing regions in both the U.S. and Canada, with the Western regions being the driest climates. The highest-temperature region is the Columbia Basin of Washington, reporting the longest growing season with the hottest and driest climate of all the researched regions.

Elevation of North American Growing Regions

Province / State	Region	Elevation (ft. above sea level
WA	Grant	Fine sand and silt loams
WA	Adams	Fine sandy loams to silt loams
ID	Jerome	Silt loams, gravelly loams
ID	Canyon	Silt loams
ID	Minidoka	Silt loams
MN	Sherburne	Fine sand
ND	Grand Forks	Silt clay loams, loams
WI	Adams	Loamy Sand, sand
MI	Ionia	Loams
MI	Montcalm	Sands and sandy loams
PA	Centre	Gravelly sandy loams
PEI		Sea Level
NB		Sea Level
QUE		1,600
ONT		1,000 - 2,100
MAN		1,000 - 2,100
SAS		700 – 4,500
ALB		4,600 – 5,300
BC		Sea Level – 5,000

Justification of Field Study Acceptance

The full intent of this paper is to provide reasonable grounds demonstrating the similarity of agro-climatic zones and to justify the acceptance of the field studies conducted with Russet Burbank Event W8 in the U.S. by Health Canada. Context concludes that this report testifies to the following factors which support the acceptance of the field studies by Health Canada:

1. A precedent has been set by Health Canada / Pest Management Regulatory Agency and the United States EPA in their regulatory decisions affecting maximum allowable pesticide residues. The precedent can be extended to Event W8.
2. The nature of potato production in the Northern U.S. and Canada is contiguous.
3. There is similarity in county and provincial soil factors affecting crop fertility management.
4. There are shared IPM practices regarding cultivar selection and disease, insect, and weed control practices.
5. Disease incidence and seasonal factors affecting number of cover sprays is similar between regions.

6. There is shared knowledge and transfer of information, related to potato production and management, across political boundaries (Source: plantmanagement.com).
7. Choices by growers are similar regarding agricultural practices such as tillage, irrigation, crop rotation, and harvest times.

Administrative requirements that explicitly require repetition of studies will significantly delay adoption of crop technologies and improvements in crop productivity. These additional studies are not necessary and are unlikely to add any new information or insights upon which an informed decision can rely.

The protection goals of Health Canada / Pest Management Regulatory Agency can be met by the weight of evidence provided in this document, and if deficiencies are present may the agency please specifically state the concerns they possess. Essentially, from the level of evidence provided in this document it can be proposed that the field trials conducted in the U.S. with Event W8 are legitimate, and the results can be extrapolated for the Canadian production regions because of the similarities previously outlined. Through the conducted field trials, no inadvertent effects have been associated with Event W8 in the U.S. and this conclusion can reasonably be used by Health Canada in accepting the field trial results.

Appendix: *Table 1: Major Characteristics of Field Location Sites*

State	County	Elevation	Soil Types	Major Pests			Control Practices of Pests	Fertility Practices	Agronomic Practices	Climate
				Insects	Weeds	Disease				
WA	Grant	<900 ft	Fine sand and silt loams	• Beet Leafhopper • Potato Psyllids • Aphids • Potato Tuberworm	• Hairy Nightshade • Russian Thistle • Red Root Pigweed • Lambs-quarters	• Late Blight (uncommon) • Early Blight (more common) • White Mold (standard)	Full season producers will: • **Pre-plant:** Fumigate • **Planting:** Neonicotinoid insecticide (has managed CPB well and made it a secondary pest) • **After row closure:** fungicide	Longer growing season requires more NPK because the canopy needs maintained 30-50 days longer	100% of production is irrigated	8 inches of rainfall with higher temperatures and low elevation
WA	Adams	<900 ft	Fine sandy loams to silt loams							
ID	Jerome	3,700 ft	Silt loams, gravelly loams	• Psyllids (zebra chip)	• Kosha (glyphosphate restance) • Nightshade	•Late blight (haven't experienced for years but still a concern) •Early Blight (moderate pressure	Arid environment makes the late blight a lower risk vs. moist east coast regions. Fungicide use is lower here though chemicals for psylid management is higher in ID	Calterea soils that change nutrient requirements. Also the soils are sandy to heavier with the regions effected by dairy production in the region	Region is dependent on irrigation (either surface water or wells). No irrigation is furrow applied	These regions get 8 inches of rainfall. Very arid
ID	Canyon	2,300 ft	Silt loams							
ID	Minidoka	4,200 ft	Silt loams	Same as above with potential for tuber moth	Same as above					8-9 inches of rainfall
MN	Sherburne	900 ft	Fine sand							
ND	Grand Forks	900 ft	Silt clay loams, loams							
WI	Adams	1,000 ft	Loamy Sand, sand							
MI	Ionia	700 ft.	Loams	• CO Potato Beetle • Aphids • Leaf-hoppers • Root Lesion Nematodes	• Lambs-quarter (most difficult to control) • Red root Pigweed • Grasses	• Late blight • Common Scab • Fusarium Dry Rot • Early Blight • Brown Leaf spot • Rhizoctonia	• **Pre-plant:** Prophylactic is used as a preventative • **Planting:** Seed treatment and in-furrow application • **After row closure:** Foliar application usually necessary	They have to be careful of their split applicators because they don't fertigate. Most fertilizer is applied prior to canopy closure. Growers are starting to use Slow Release and starter fertilizer	• 100% center pivot • Standard tillage practices • Growers will dam or dike to retain water in the field • 2-4 yr. rotation with wheat, corn, or soybeans • Harvest is late July through late Oct.	• Rainfall in 2014 was 24 in. where avg. is 15 • Temperature is temperate • Growing season is Early May through end of October
MI	Montcalm	1,100 ft	Sands and sandy loams							
PA	Centre	1400 ft	Gravelly sandy loams							

Supplement B

Agronomic and Phenotypic Attributes Analyzed by Site

Introduction

Agronomic studies for all sites over multiple years were summarized and submitted as Appendix 6: Field Performance and Tuber Evaluations. That analysis considers the overall question of how Innate™ events E12, F10, J3, and J55 compare with their respective controls. For the purpose of a regulatory determination for environmental safety, that summarized analysis should provide the most relevant and comprehensive comparison of the events with their controls.

This Supplement includes all statistically significant comparisons for agronomic characteristics including yield and grading between event and controls when each individual field trial was analyzed separately. For example, the analysis was conducted separately for our Aberdeen trial site in 2009, Aberdeen in 2010, Cody in 2010, and so forth. This analysis would allow for a greater likelihood to see differences should there be interactions between the genetic modification and the environment. A review of these data could provide insight into environmental safety of the events compared with the controls.

1. Agronomic Characteristics - Site by Year Combinations

As a way to focus the results of this site-specific analysis on the most important sites and event for statistical significance, the total number of differences are summarized below and shown relative to the total number of comparisons (Table 1). For example, the site with the most significant differences, 8, was Aberdeen, ID, in 2011. This overall summary shows that Larimore, ND, in 2010, and Othello, WA, 2011 each had 6 differences. The event with the most differences was J55 with 15, followed by E12 with 14. Overall, there were 48 differences with a total of 462 comparisons of event mean to control.

Table 1. Agronomic characteristics and yield and grading – number of observations and significant differences by site.

	Significant differences by site and year				Total by site/year
	E12	F10	J3	J55	
Aberdeen, ID 2009	0	1			1
Aberdeen, ID 2010	2	0	0	1	3
Aberdeen, ID 2011	2	4	2	0	8
Cody, NE 2010			0	1	1
Hancock, WI 2010			1	1	2
Hancock, WI 2011			0	2	2
Hastings, FL 2011			0	0	0
Lakeview, MI 2009	1	2			3
Lakeview, MI 2010			0	1	1
Lakeview, MI 2011			0	2	2
Larimore, ND 2010	4	0	1	1	6
Larimore, ND 2011	0	0	0	2	2
Othello, WA 2010	1	1	1	0	3
Othello, WA 2011	2	2	1	1	6
Parma, ID 2009	1	0			1
Parma, ID 2010	1	0	1	1	3
Parma, ID 2011	0	1	0	1	2
Winamac, IN 2011			1	1	2
Total Significant Differences	14	11	8	15	48
Total Comparisons	102	102	129	129	462

= The site was not used for that event in that year.

A summary of significant differences overall for agronomic characteristics is shown in Table 2. The agronomic characteristics most likely to be different were early emergence, stems per plant, plant vigor, and vine maturity. Overall, there were 33 significant comparisons out of a total of 260.

Table 2. Agronomic characteristic observations for all sites over multiple years.

	E12		F10		J3		J55		Grand Total	
Characteristic	#Sites	Sig	Sites	Sig	Sites	Sig	Sites	Sig	Sites	Sig
1) Early emergence	4	0	4	0	13	4	13	4	34	8
2) Final emergence	10	1	10	1	6	0	6	0	32	2
3) Stems per plant	4	1	4	1	6	2	6	3	20	7
4) Plant vigor	11	3	11	3	12	0	12	0	46	6
5) Foliage color	10	1	10	0	10	0	10	0	40	1
6) Leaflet size	8	2	8	0	6	0	6	0	28	2
7) Leaflet curl	4	0	4	1	3	0	3	0	14	1
8) Senescence	3	0	3	0	5	0	5	0	16	0
9) Vine maturity	7	3	7	1	8	0	8	2	30	6
Total comparisons	61	11	61	7	69	6	69	9	260	33

Sig = # of statistical differences between the event and the conventional control.

In addition to the summary information (Tables 1 and 2), all significant differences that were observed for each variety, site, year, and agronomic characteristic are summarized in Table 3. Note that more characteristics were assessed in 2010 and 2011 than in 2009 in order to better assess the phenotype. The discussion that follows covers all the significant differences by variety (Table 3).

Table 3. Agronomic Characteristics Significant Differences By-Site.

Year	State	Site	Variety	Characteristic	Mean	p-Value	SD	N
2010	WA	Othello	Russet Burbank E12	Final Emergence	0.8	0.0250	0.1	3
			Russet Burbank Control		1.0		0.1	3
2011	WA	Othello	Russet Burbank E12	Stems Per Plant	3.0	0.0001	0.1	3
			Russet Burbank Control		2.7		0.0	3
2009	MI	Lakeview	Russet Burbank E12	Plant Vigor	3.5	0.0228	0.4	5
			Russet Burbank Control		3.0		0.0	5
2010	ID	Aberdeen	Russet Burbank E12	Plant Vigor	3.7	0.0336	0.6	3
			Russet Burbank Control		3.0		0.0	3
2010	ND	Larimore	Russet Burbank E12	Plant Vigor	4.0	0.0323	1.0	3
			Russet Burbank Control		3.0		0.0	3
2010	ND	Larimore	Russet Burbank E12	Foliage Color	3.7	0.0054	0.6	3
			Russet Burbank Control		3.0		0.0	3
2010	ND	Larimore	Russet Burbank E12	Leaflet Size	3.3	0.0142	0.6	3
			Russet Burbank Control		3.0		0.0	3
2011	WA	Othello	Russet Burbank E12	Leaflet Size	2.7	0.0006	0.6	3
			Russet Burbank Control		2.0		0.0	3
2009	ID	Parma	Russet Burbank E12	Vine Maturity Rating	3.7	0.0034	0.4	5

			Russet Burbank Control		3.0		0.0	5
2010	ID	Parma	Russet Burbank E12	Vine Maturity Rating	3.7	0.0313	0.6	3
			Russet Burbank Control		3.0		0.0	3
2010	ND	Larimore	Russet Burbank E12	Vine Maturity Rating	4.7	<.0001	0.6	3
			Russet Burbank Control		3.0		0.0	3
2009	MI	Lakeview	Ranger Russet F10	Final Emergence	0.9	0.0496	0.1	5
			Ranger Russet Control		1.0		0.1	5
2011	WA	Othello	Ranger Russet F10	Stems Per Plant	2.5	0.0280	0.2	3
			Ranger Russet Control		2.4		0.0	3
2009	ID	Aberdeen	Ranger Russet F10	Plant Vigor	3.6	0.0029	0.4	5
			Ranger Russet Control		3.0		0.0	5
2011	ID	Aberdeen	Ranger Russet F10	Plant Vigor	3.5	0.0008	0.9	3
			Ranger Russet Control		2.3		0.6	3
2011	ID	Parma	Ranger Russet F10	Plant Vigor	3.7	0.0176	0.6	3
			Ranger Russet Control		2.7		0.6	3
2009	MI	Lakeview	Ranger Russet F10	Leaflet Curl	1.6	0.0279	0.9	5
			Ranger Russet Control		1.0		0.0	5
2010	WA	Othello	Ranger Russet F10	Vine Maturity Rating	1.7	0.0480	0.6	3
			Ranger Russet Control		3.0		0.0	3
2010	ID	Aberdeen	Atlantic J55	Early Emergence	0.6	0.0109	0.2	5
			Atlantic Control		0.9		0.1	5
2010	ID	Parma	Atlantic J3	Early Emergence	0.4	0.0267	0.1	3
			Atlantic Control		0.8		0.3	3
2010	MI	Lakeview	Atlantic J55	Early Emergence	0.4	0.0379	0.1	3
			Atlantic Control		0.3		0.1	3
2010	ND	Larimore	Atlantic J3	Early Emergence	0.5	0.0018	0.2	5
			Atlantic Control		0.1		0.1	5
2010	NE	Cody	Atlantic J55	Early Emergence	0.6	0.0042	0.1	5
			Atlantic Control		0.9		0.1	5

2010	WA	Othello	0.0265	0.1	5			
Atlantic J3	Early Emergence		Atlantic Control		0.6		0.1	5
2010	WI	Hancock	Atlantic J3	Early Emergence	0.8	0.0253	0.1	5
			Atlantic J55		0.7	0.0009	0.1	5
			Atlantic Control		0.9		0.1	5
2011	ID	Parma	Atlantic J55	Stems Per Plant	2.0	0.0471	0.2	3
			Atlantic Control		1.6		0.2	3
2011	IN	Winamac	Atlantic J3	Stems Per Plant	5.7	0.0004	0.2	3
			Atlantic J55		5.2	0.0056	0.1	3
			Atlantic Control		4.5		0.3	3
2011	WA	Othello	Atlantic J3	Stems Per Plant	2.3	0.0006	0.1	3
			Atlantic J55		2.3	0.0006	0.1	3
			Atlantic Control		2.6		0.1	3
2010	ID	Parma	Atlantic J55	Vine Maturity Rating	3.7	0.0313	0.6	3
			Atlantic Control		3.0		0.0	3
2010	ND	Larimore	Atlantic J55	Vine Maturity Rating	4.6	<.0001	0.5	5
			Atlantic Control		3.0		0.0	5

1.1 Russet Burbank Variety

No statistically significant differences were observed between Russet Burbank E12 and the Russet Burbank control for early emergence, leaflet curl, or senescence.

Statistically significant differences between E12 and the control were observed for the following agronomic characteristics: Of a total of 61 evaluations for E12, the following 11 were different.

- Fewer plants emerged for E12 at Othello, WA in 2010.
- E12 produced more stems per plant at Othello, WA in 2011.
- E12 was more vigorous at Aberdeen, ID in 2010, Larimore, ND in 2010, and Lakeview, MI in 2009.
- E12 foliage was judged as darker at Larimore, ND in 2010.
- E12 grew larger leaflets at Larimore, ND in 2010 and Othello, WA in 2011.
- E12 vines matured faster at Larimore, ND in 2010, Parma, ID in 2009, and Parma, ID in 2010.

1.2 Ranger Russet Variety

No statistically significant differences were observed between Ranger Russet F10 and the Ranger Russet control for early emergence, foliage color, leaflet size, or senescence.

Statistically significant differences between F10 and the control were observed for the following agronomic characteristics: Of a total of 61 evaluations for F10, the following 7 were different.

- Fewer plants emerged for F10 at Lakeview, MI in 2009.
- F10 produced more stems per plant at Othello, WA in 2011.
- F10 was more vigorous at Aberdeen, ID in 2009 and 2011, and Parma, ID in 2011.
- F10 leaflets were curlier at Lakeview, MI in 2009.
- F10 vines matured more slowly at Othello, WA in 2010.

1.3 Atlantic Variety J3

No statistically significant differences were observed between Atlantic J3 and the Atlantic control for final emergence, plant vigor, foliage color, leaflet size, leaflet curl, senescence, or vine maturity.

Statistically significant differences between J3 and the control were observed for the following agronomic characteristics: Of a total of 69 evaluations for J3, the following 6 were different.

- J3 emerged slower at Parma, ID in 2010, Othello, WA in 2010 and Hancock, WI in 2010. J3 emerged faster at Larimore, ND in 2010.
- J3 produced fewer stems per plant at Othello, WA in 2011 and more stems per plant at Winamac, IN in 2011.

1.4 Atlantic Variety J55

No statistically significant differences were observed between Atlantic J55 and the Atlantic control for final emergence, plant vigor, foliage color, leaflet size, leaflet curl, or senescence.

Statistically significant differences between J55 and the control were observed for the following agronomic characteristics: Of a total of 69 evaluations for J55, the following 9 were different.

- J55 emerged slower at Aberdeen, ID in 2010, Cody, NE in 2010, and Hancock, WI in 2010. J55 emerged faster at Lakeview, MI in 2010.
- J55 produced fewer stems per plant at Othello, WA in 2011 and more stems per plant at Parma, ID in 2011 and Winamac, IN in 2011.
- J55 vines matured faster at Parma, ID in 2010 and Larimore, ND in 2010.

1.5 Agronomic Characteristics Conclusions

Overall, the data analysis showed 33 statistically significant differences out of a total of 260 site x agronomic characteristic combinations between events E12, F10, J3, J55 and their respective controls. Although differences were observed, there were no clear trends that appear site related. Therefore, these site related differences are unlikely to signal an altered observed phenotype between E12, F10, J3, J55, and their respective controls.

2. Yield and Grading Characteristics - Site by Year Combinations

The Russet Burbank and Ranger Russet varieties are typically grown for frozen french fries and were graded as if used for those purposes. Grading standards differ for chipping varieties like Atlantic and will be summarized separately. The following yield and grading characteristics were observed for Russet Burbank Variety E12 and Ranger Russet Variety F10 (french fry varieties) across multiple sites and years (Table 4):

Table 4. Yield and grading observations for all sites over multiple years (E12 and F10).

	E12		F10		Grand Total	
Characteristic (E12, F10)	**Sites**	**Sig**	**Sites**	**Sig**	**Sites**	**Sig**
1) Total yield	9	1	9	1	18	2
2) % 4-6 oz. tubers	4	1	4	1	8	2
3) % 6-10 oz. tubers	4	0	4	0	8	0
4) % 10-14 oz. tubers	4	1	4	1	8	2
5) % > 14 oz. tubers	4	0	4	1	8	1
6) Specific gravity	4	0	4	0	8	0
7) % high sugar	4	0	4	0	8	0
8) % sugar ends	4	0	4	0	8	0
9) % total internal defects	4	0	4	0	8	0
Total Comparisons	41	3	41	4	82	7

Sig = # of statistical differences between the event and the conventional control.

The following yield and grading characteristics were observed for Atlantic Variety J3 and J55 (chipping varieties) across multiple sites and years (Table 5):

Table 5. Yield and grading observations for all sites over multiple years (J3 and J55).

	J3		J55		Grand Total	
Characteristic (J3, J55)	**Sites**	**Sig**	**Sites**	**Sig**	**Sites**	**Sig**
1) Total yield	8	0	8	0	16	0
2) US#1 yield	8	0	8	1	17	4
3) Grade A	8	0	8	0	16	0
4) Grade B	8	1	8	2	19	3
5) Oversize	7	0	7	1	15	1
6) Pick outs	5	0	5	1	11	1
7) Specific gravity	8	1	8	1	18	2
8) Total internal defects	8	0	8	0	16	0
9) Total Comparisons	60	2	60	6	120	8

Sig = # of statistical differences between the event and the conventional control.

In this Supplement, significant differences are summarizes for yield and grading characteristics for each variety, site, and year combination (Table 4, Table 5, and Table 6). Note that more characteristics were assessed in 2010 and 2011 than in 2009 as changes were made to assess the phenotype better. The discussion that follows covers all the significant differences by variety which are detailed in Table 6.

Table 6. Yield and Grading Characteristics Significant Differences By-Site.

Year	State	Site	Variety	Characteristic	Mean		SD	N
2010	ID	Aberdeen	Russet Burbank E12	Total Yield	36.7	0.0358	1.5	3
			Russet Burbank Control		42.7		2.1	3
2011	ID	Aberdeen	Russet Burbank E12	4-6 oz. Tubers	28.4	0.0195	3.8	3
			Russet Burbank Control		20.9		4.5	3
2011	ID	Aberdeen	Russet Burbank E12	10-14 oz. tubers	7.9	0.0165	1.6	3
			Russet Burbank Control		18.0		8.6	3
2011	WA	Othello	Ranger Russet F10	Total Yield	45.7	0.0083	5.5	3
			Ranger Russet Control		59.0		4.0	3
2011	ID	Aberdeen	Ranger Russet F10	4-6 oz. tubers	22.2	0.0007	2.5	3
			Ranger Russet Control		9.2		1.1	3
2011	ID	Aberdeen	Ranger Russet F10	10-14 oz. tubers	14.9	0.0215	4.3	3
			Ranger Russet Control		24.5		5.0	3
2011	ID	Aberdeen	Ranger Russet F10	> 14 oz. tubers	11.9	0.0141	8.6	3
			Ranger Russet Control		29.4		9.6	3
2011	ID	Aberdeen	Atlantic J3	Grade B	6.3	0.0215	1.5	3
			Atlantic Control		3.0		1.7	3
2011	ID	Aberdeen	Atlantic J3	Specific Gravity	1.092	0.0031	0.002	3
			Atlantic Control		1.090		0.001	3
2011	MI	Lakeview	Atlantic J55	Grade US#1	78.0	0.0167	3.2	4
			Atlantic Control		82.5		2.1	4
2011	MI	Lakeview	Atlantic J55	Grade B	22.0	0.0167	3.2	4
			Atlantic Control		17.5		2.1	4

2011	WA	Hancock	0.0335	3.8	3			
Atlantic J55	Grade B		Atlantic Control		12.3		0.6	3
2011	WI	Hancock	Atlantic J55	Oversize	14.0	0.0158	5.3	3
			Atlantic Control		5.3		1.5	3
2011	ND	Larimore	Atlantic J55	Pick Outs	0.0	0.0498	0.0	3
			Atlantic Control		0.7		0.6	3
2011	ND	Larimore	Atlantic J55	Specific Gravity	1.109	0.0193	0.002	3
			Atlantic Control		1.104		0.002	3

2.1 Russet Burbank Variety

No statistically significant differences were observed between Russet Burbank E12 and the Russet Burbank control for % 6-10 oz. tubers, % > 14 oz. tubers, specific gravity, % high sugar, % sugar ends, and % total internal defects.

Statistically significant differences between E12 and the control were observed for the following yield and grading characteristics: Of a total of 41 evaluations for E12, the following 3 were different.

- E12 had lower total yield at Aberdeen, ID in 2010.
- E12 produced more 4-6 oz. tubers at Aberdeen, ID in 2011.
- E12 produced fewer 10-14 oz. tubers at Aberdeen, ID in 2011.

2.2 Ranger Russet Variety

No statistically significant differences were observed between Ranger Russet F10 and the Ranger Russet control for % 6-10 oz. tubers, specific gravity, % high sugar, % sugar ends, and % total defects.

Statistically significant differences between F10 and the control were observed for some yield and grading characteristics: Of a total of 41 evaluations for F10, the following 4 were different.

- F10 had lower total yield at Othello, WA in 2011.
- F10 produced more 4-6 oz. tubers at Aberdeen, ID in 2011.
- F10 produced fewer 10-14 oz. tubers at Aberdeen, ID in 2011.
- F10 produced fewer >14 oz. tubers at Aberdeen, ID in 2011.

2.3 Atlantic Variety J3

No statistically significant differences were observed between Atlantic J3 and the Atlantic control for total yield, % US #1, % grade A, % oversize, % pick outs, and % total internal defects.

Statistically significant differences between J3 and the control were observed for some yield and grading characteristics: Of a total of 60 evaluations for J3, the following 2 were different.

- J3 produced more grade B tubers at Aberdeen, ID in 2011.
- J3 tubers had lower specific gravity at Aberdeen, ID in 2011.

2.4 Atlantic Variety J55

No statistically significant differences were observed between Atlantic J55 and the Atlantic control for total yield, % grade A tubers, specific gravity, and % total internal defects.

Statistically significant differences between J55 and the control were observed for some yield and grading characteristics: Of a total of 60 evaluations for J55, the following 6 were different.

- J55 produced fewer US #1 tubers at Lakeview, MI in 2011.
- J55 produced fewer grade B tubers at Hancock, WI in 2011 and more grade B tubers at Lakeview, MI in 2011
- J55 produced more oversize tubers at Hancock, WI in 2011
- J55 produced fewer pick outs at Larimore, ND in 2011
- J55 had higher specific gravity at Larimore, ND in 2011

2.5 Yield and Grading Conclusions

Overall, the data analysis showed 15 statistically significant differences out of a total of 202 site x yield and grading characteristic combinations between E12, F10, J3, J55 and their respective controls. Although differences were observed, there were no clear trends that appear site related. Therefore, these site related differences are unlikely to signal an altered observed phenotype between E12, F10, J3, J55, and their respective controls.

3.0 Conclusions: Agronomic, Phenotypic, Attributes Analyzed by Site

As noted in Section 7.8 of the original submission, submitted for events E12, F10, J3, and J55, some of the events showed reduced yield along with greater numbers of smaller potatoes and fewer large potatoes. These observations, if they persist with commercial production, would not contribute to weediness, or affect the ability for these events to become plant pests, influence gene flow, or impact on other organisms, including humans, or affect biodiversity.

Supplement C

Polyphenol Oxidase in Plant Disease and Insect Susceptibility

(update of Chapter 8 of the original submission)

Disease Susceptibility in the Events

Studies were conducted to confirm that transformation with pSIM1278 did not alter the disease susceptibility of events F10, E12, J3, and J55. Some researchers have hypothesized that the silencing of polyphenol oxidases can either enhance or reduce disease susceptibility. Late blight and *Erwinia* studies were conducted and confirmed that events F10, E12, J3, and J55 have similar disease susceptibility as the appropriate controls.

8.1 Polyphenol Oxidase

Polyphenol oxidase enzymes (Ppos) are found in most organisms including animals, plants, fungi and bacteria. Although much is known about the molecular biology of Ppo and its role in enzymatic browning, little is understood about the function of Ppo-mediated browning in plant physiology. Some have hypothesized that Ppos represent part of the plant's defense response against insects and pathogens. Considering that the present submission involves silencing of Ppo in tubers, we reviewed relevant literature and conducted studies relating to the disease response of the events.

Ppos are copper metalloenzymes which oxidize mono- and o-diphenols to o-diquinones by utilizing molecular oxygen (Thipyapong *et al.* 2004), which are then further oxidized non-enzymatically to polyphenols. These dark-pigmented polyphenols, also referred to as melanins, result in the darkening of potato tissue following mechanical bruising (Thygesen, Dry, & Robinson, 1995).

Typically, Ppo activity is latent until the enzyme is released by disruption of the cell structure through forces like wounding and senescence. When cell membranes are damaged, Ppo enzyme is released and reacts with oxygen molecules to produce quinones (Thipyapong *et al.* 2004). The production of black and brown quinones is responsible for much of the interest in PPO in the post-harvest physiology of many fruit and vegetable crops.

In potato, Ppo is involved in black spot formation, which reduces the quality of harvested tubers (Bachem, et al., 1994) (Corsini, Stark, & Thornton, 1999) (Partington, Smith, & Bolwell, 1999). Impacts sustained during harvest and postharvest activities induce the release of Ppo from cell plastids, facilitating oxidation of phenolic compounds to quinones, and resulting in negative effects on quality and recovery in french fry and chip processing, as well as the marketability of fresh potatoes.

It is common for multiple homologues or alleles to exist within species, each responsible for expression in different plant tissues. In potato, six genes encoding Ppo have been identified, tomato (*Lycopersicon esculentum*) possesses 7 Ppo genes, and banana (*Musa acuminata*) is known to contain a Ppo family of at least four genes (Thipyapong *et al.* 2007; Mayer 2006). Of the family of six genes encoding Ppo in potato, the *Ppo5* gene is tuber-specific and the remaining five genes are responsible for Ppo expression in other tissues. The tuber-specific *Ppo5* gene was down-regulated, resulting in reduced susceptibility to black spot bruise, as shown in the original submission.

Researchers found that by down-regulating Ppo activity in potato (*e.g.*, see Hakimi *et al.* 2006), disease

symptoms of *P.infestans* were reduced, apparently corresponding to an increase in the plant's resistance to late blight. The authors proposed that tubers may also display enhanced disease resistance against certain other fungal pathogens that infect potato tubers, including *Rhizoctonia* (black scurf), *Fusarium* (dry rot), *Spongospora* (powdery scab) and *Alternaria* (early blight).

A number of researchers evaluated induced Ppo activity and response mechanisms to biotic stressors, in particular pests and pathogens (Steffens *et al.* 1994). Studies with biotech tomatoes found a positive correlation between high levels of Ppo in leaf tissue and increased resistance to pathogens and insect pests. In one study, three lines with higher Ppo expression were tested against the bacterial pathogen *Pseudomonas syringae* pv. *tomato*, the causal agent of bacterial speck in tomato (Li and Steffens 2002). These lines showed enhanced suppression of disease symptoms and exhibited 15-fold fewer lesions per leaf area than controls. Although these results indicated a protective effect of Ppo, the mechanism for disease resistance remains unknown (Li and Steffens 2002).

Phenolic compounds, the substrates for polyphenol oxidase enzymes, occur in a wide distribution of plants (Felton, Donato, Del Vecchio, & Duffey, 1989), but their biological function remains unclear (Bachem, et al., 1994) (Mayer, 2006). The oxidation products of Ppo, resulting from a reaction with phenolic compounds, appear to play a role in general plant defense mechanisms against pathogens and pests. The relationship between Ppo and resistance to herbivores has also been studied. Ppo activity increases when potato leaves are wounded and in response to regurgitant from the pest Colorado potato beetle (Kruzmane, Liga, & Ievinsh, 2002). In other plants, the increase of Ppo activity is a direct induced defense against insect pests that decreases nutrient availability (Baldwin & Preston, 1999) (Partington, Smith, & Bolwell, 1999). In addition, Ppo in glandular trichomes of wild potatoes (and other plants) is involved in resistance to insects (Steffens, 1994) (Plaisted, 1980). However, the trichomes (physicochemical defense mechanism against insects) of cultivated potatoes contain low amounts of Ppo which is not thought to be involved resistance to pests (Friedman M. , 1997). Phylogenetic surveys of Ppo in land plants shows that the gene family has undergone evolutionary expansion in some plant families, but is reduced or absent in others, which suggests that Ppo function is probably diverse (Tran, Taylor, & Constabel, 2012). Ppo has also been implicated in other functions such as buffering of plastid oxygen levels, wound healing, and chloroplast metabolism (Steffens, 1994).

Nematode damage was not assessed in Simplot events E12, F10, J3, and J55, but Osman et al. (2012) suggest that Ppo might be involved in resistance to some plant parasitic nematodes, but do not provide data demonstrating such a role or address the species that affect potatoes. Conversely, lower Ppo levels might increase the resistance of Simplot E12, F10, J3, and J55 potatoes to some nematodes. Other researchers found that tubers of potato cultivars resistant to the potato cyst nematode, *Globodera pallida,* have lower levels of phenols and discolored less than tubers of susceptible cultivars (Mondy, Chandra, & Evans, 1985). They suggest that Ppo-mediated tanning of nematode cysts enables eggs to remain viable in soil for a longer time. Lyon (1989) reviewed the biochemical basis for resistance of potato to bacterial soft rot caused by *Erwinia* spp. Because it is the dominant monophenol, chlorogenic acid has been a focus in many of these studies. Chlorogenic acid did not inhibit the *in vitro* growth of *Erwinia* spp. or *P. infestans* (the causal agent of late blight), and there remains no proof that phenols are important in the interaction between potato and *Erwinia* spp. (Lyon, 1989).

Kroner and Marnet (2012) evaluated the role of specific phenolics in quantitative resistance to the elicitors of two pathogens, *P. infestans*, the causal agent of late blight, and *Pectobacterium atroseptiucm* (synonym: *E. carotovora* subsp. *atroseptica*), the causal agent of bacterial soft rot. Increasing concentrations of total phenolics tended toward a positive correlation with quantity of symptoms due to

the late blight pathogen, but were negatively correlated with increased tuber rot severity due to the soft rot pathogen. Because chlorogenic acid accumulates in response to soft rot elicitors, these authors suggest that chlorogenic acid could be used as a marker for resistance to soft rot (Kroner & Marnet, 2012). Since chlorogenic acid is a Ppo substrate, silencing of Ppo would not be expected to reduce the level of chlorogenic acid in potato tubers.

Enzymatic browning is an important reaction that occurs in the fruit of the apple (*Malus domestica*). In a study conducted by Valentines *et al.* (2005), the roles of enzymatic browning and lignification (the chemical strengthening of cell walls in response to pathogenic infection) as resistance mechanisms against *Penicillium expansum* were investigated in Golden Delicious apples. A significant increase in decay was observed following the treatment of peeled apples with a Ppo substrate which had induced higher Ppo activity levels. The Ppo enzyme, and particularly the browning process induced by treatment with Ppo substrate, may have contributed to increase decay and indicates that an overexpression of Ppo may lead to higher level of sensitivity towards the pathogen (Valentines *et al.* 2005).

Some researchers have proposed that enhanced Ppo may increase resistance to disease, while others claim that reduced Ppo could also increase resistance. Considering that some evidence exists for a relationship between Ppo and diseases, we chose to test the events for several important potato diseases and conclude that there is no impact on disease resistance or susceptibility with regards to the *Ppo5* gene as demonstrated in the remainder of this section.

8.2 Disease Incidence: Late Blight and Bacterial Soft Rot

Disease incidence was evaluated by intentionally infecting the events and their untransformed controls with the causal agents of late blight (*Phytophthora infestans*) and soft rot (*Erwinia carotovora*) and evaluating disease progression. Details regarding the following tests are included in Appendix 8: Disease Susceptibility.

Late Blight Testing with Tubers. Using tubers from the 2011 field season, event E12 was found to be less susceptible to late blight than controls. In addition, Atlantic event J3 was found to be more susceptible than Atlantic controls; however, J3 was similar to Ranger Russet and Russet Burbank controls. Ranger Russet event F10 did not differ from its control (Table 24). The Atlantic Control had a lower percentage disease than either Russet Burbank or Ranger Russet controls, suggesting that Atlantics may have more natural resistance to this pathogen. Overall results were variable with no consistent pattern: E12 showing less disease and J3 more disease than their respective controls. The results suggested that the pSIM1278 insert does not influence susceptibility to late blight infection in tubers.

Table 24. Late Blight Symptoms in Tubers of Ranger Russet, Russet Burbank and Atlantic Events[1]

Line	Avg. Disease %	P-value[2]
Russet Burbank Control	74.50	0.0296
E12	23.50	
Ranger Russet Control	65.50	0.6466
F10	71.65	
Atlantic Control	11.50	
J3	73.50	0.0024
J55	43.60	0.0919

[1]Data in this table are from tubers harvested in 2011.

[2]P-values were determined with Tukey-Kramer HSD analyses with a significance level of $P < 0.05$. P-values indicating significant differences with controls are underlined.

Late Blight Foliage Testing. In a replicated field trial in 2011, potato plants were deliberately infected with the causal agent, *P. infestans*. Of the events in that trial, the only significant difference was that event F10 was more resistant than the control. This replicated field trial provides evidence that events were no more susceptible to late blight than the untransformed controls (Table 25). As with testing of tubers, the foliar tests with F10 showed less late blight disease than the Ranger Russet controls, suggesting that no consistent pattern exists to indicate that the pSIM1278 insert influences susceptibility to late blight infection in potato foliage.

Table 25. Late Blight Symptoms in Foliage of Ranger Russet, Russet Burbank and Atlantic Events[1]

Line	RAUDPC[2]	P-value[3]
Burbank Control	21.9	
E12	19.9	0.8361
Ranger Control	24.3	
F10	17.3	<u><0.0001</u>
Atlantic Control	33.6	
J3	35.8	0.6929
J55	33.7	0.9999

[1]Data in this table are from 2011 disease analyses.
[2]Relative Area Under the Disease Progression Curve (RAUDPC x100) (see Disease Susceptibility Appendix)
[3]P-values determined with Tukey-Kramer HSD analyses with a significance level of $P < 0.05$. P-values indicating significant differences with controls are underlined.

Soft Rot Testing with Tubers. A test with tubers in 2009 showed a similar response to Erwinia infection between Russet Burbank and Event E12 (Table 26). Further testing in 2011 of all events showed that Atlantic events J3 and J55 were less susceptible than untransformed controls (Table 27). Considering both studies, we conclude that events E12, F10, J3, and J55 have no consistent difference in susceptibility to bacterial soft rot when compared with the controls.

Table 26. Weight Loss (%) in *Erwinia*-infected Tubers in 2009

Line	Mean Weight Loss ± Std. Error[1]
Burbank Control	1.474 ± 0.589
E12	1.161 ± 0.200

[1]Based on a comparison of means and their associated Std. Errors, no differences were observed between the events and their untransformed counterparts.

Table 27. Weight Loss (%) in *Erwinia*-infected Tubers in 2011

Line	Mean Weight Loss (%)	Range (%)	P-value[1]
Ranger Control	1.80	1.19-2.40	
F10	1.81	1.37-2.24	0.9604
Burbank Control	2.04	1.73-2.61	

E12	1.57	1.19-1.86	0.1520
Atlantic Control	3.30	2.39-4.67	
J3	2.73	2.33-3.21	0.0153
J55	2.67	2.24-3.43	0.0085

[1]P-values determined using Tukey-Kramer HSD with a significance level of $P < 0.05$. P-values indicating significant differences with controls are underlined.

The silencing strategy, using AGP and GBSS promoters, deliberately targeted silencing in tubers and not the whole plant. By targeting the tuber specific *Ppo5* gene, Ppo gene expression and Ppo levels in leaves were unchanged. Thus, potential interactions between potato foliar Ppo and foliar pathogens or pests in events E12, F10, J3, and J55 were expected to be unchanged. No consistent differences were observed in foliar pest and pathogens on events F10, E12, J3, and J55 compared to their control varieties.

8.3 Conclusions: Disease Susceptibility in the Events

The studies with late blight and bacterial soft rot confirm that silencing of the target genes did not enhance susceptibility to these common diseases. Silencing of the polyphenol oxidase enzyme does not appear to affect disease susceptibility in events F10, E12, J3, and J55. However, if any events showed slightly higher susceptibility to disease, it would not enhance the weediness or result in the creation of plant pests.

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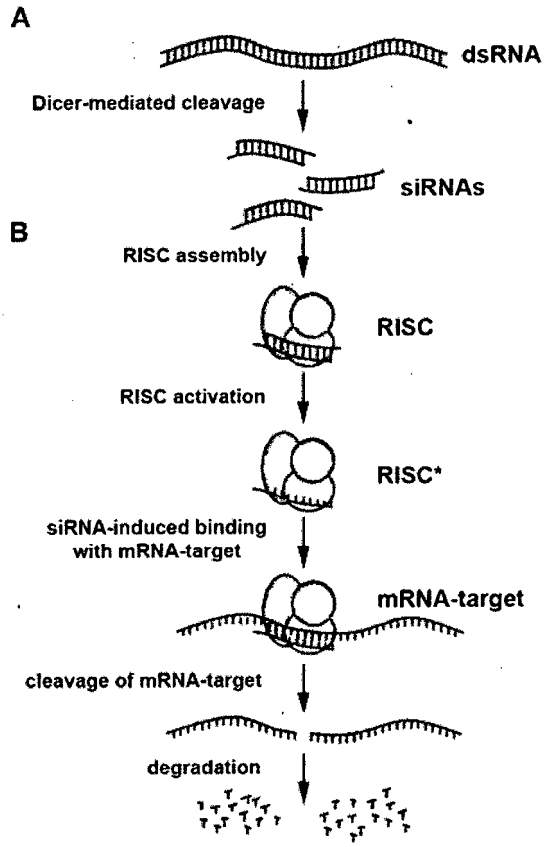
Supplement D

Analysis of pSIM1278 siRNA Targets and Specificity

(Supplement in response to CFIA PBRA questions from September 2, 2014 and Health Canada questions from August 27, 2014)

Analysis of pSIM1278 siRNA Targets and Specificity

Figure 1 Schematic of RNAi (Petrova et al., 2013).



Cellular gene expression is tightly regulated in cells at both the transcriptional and post-transcriptional levels. RNA interference (RNAi) is one of nature's post-transcriptional regulatory pathways used to limit expression of a particular gene. The mechanism is initiated by a double-stranded RNA (dsRNA) precursor that contains sequence corresponding to a target messenger RNA (mRNA) in the cell. In general, half of the dsRNA molecule matches a target gene and the other half consists of complementary sequence. A cellular RNase III enzyme, Dicer, recognizes and processes the longer dsRNA molecule into small 21 bp duplexes consisting of two individual strands termed siRNA (Figure 1A). These siRNA duplexes are subsequently bound by the RNA Induced Silencing Complex (RISC), which selectively degrades one of the two strands, referred to as the passenger strand (Figure 1B, red). The remaining strand, referred to as the guide strand (Figure 1B, blue), serves to activate RISC and turn it into a silencing complex. The activated RISC destroys those mRNA that it contacts, in which the retained siRNA has complete complementarity with the mRNA (Figure 1B).

The cleavage of these target RNAs can lead to reduced expression of the associated protein, but silencing efficiencies can vary dramatically for individual siRNA (Petrova, Zenkova, & Chernolovskaya, 2012). Some organisms, including plants, possess a related process where an RNA-Dependent RNA Polymerase (RdRP) uses the cleaved mRNA as a template to generate additional siRNAs (22 nts) referred to as secondary (2°) siRNA, which also have the potential to silence the target message.

Although a single siRNA is sufficient to direct cleavage of an mRNA, not all siRNAs are equally effective at cleaving mRNA. For this reason, it has become common when working with plants to design inverted repeats with stem regions containing 100-1000 base pairs (bp) to serve as silencing triggers (Hirai & Kodama, 2008). The transcription product of the inverted repeat is an

intramolecular double-stranded RNA structure that is processed by Dicer into siRNA duplexes as described in Figure B.1.

The use of bioinformatics assessments to identify off-target effects in plant biotechnology has been controversial due to limitations and challenges associated with data interpretation. There are numerous limitations to these approaches, most of which lead to over representation of the number of off-targets. Based upon many experimental observations, we know that not all of the siRNAs in cells are stable and effective at inducing silencing and that identity between siRNAs and sequences in a database does not necessarily predict productive interactions. Nonetheless, in this study we have performed an exhaustive analysis of all potential siRNA that could arise as a result of processing the pSIM1278 inverted repeats with the mRNA targets contained in the Michigan State University (MSU) transcript reference database for potatoes (Sharma et al., 2013). The predicted off-target RNAs identified should be considered with the following caveats in mind:

1. As mentioned earlier and shown in Figure 1B, each siRNA duplex consists of a guide strand and a passenger strand. The passenger strands do not have silencing potential as they are selectively degraded prior to RISC activation. Thus, only half of the siRNAs that can be computationally predicted fall into the class of guide strands with the potential to direct mRNA target destruction. Bioinformatics approaches, such as the one described in this report, do not distinguish between guide and passenger strands, which means that the predicted target binding sites significantly over-represent the actual binding sites due to inclusion of passenger siRNA:mRNA interactions. As a result, the number of target interactions described is two-fold higher than might be observed empirically.

2. Expression of Innate™ siRNA are limited to tubers and don't appear to spread significantly within the plant. Thus, a target RNA must be expressed in the tuber with the siRNA for it to be silenced by the siRNAs generated from our inverted repeats, once again indicating that the siRNA off-targets identified in our analysis likely over-represent the number of real off-targets.

3. Although complementarity between siRNAs and potential targets is important for specificity, it is generally appreciated that there are contextual effects of nearby sequence on the target RNA. That is, sequences distinct from the siRNA binding site on the target RNA can prohibit or promote target silencing (Liu, Li, Lin, & Zuo, 2013; Luo & Chang, 2004; Overhoff et al., 2005). The local effects are complicated and not fully understood, which makes it challenging to identify which RNAs with complementarity are legitimate off-targets. It is possible the number of targets predicted by bioinformatics will over-represent the actual number of off-targets.

4. The relative abundance of siRNAs and all potential targets will also influence silencing potential. RNAs that are low in abundance are less likely to be silenced in the presence of the abundant targets based upon binding kinetics – again leading to over-representation of siRNA targets.

5. Mechanisms such as compensatory transcriptional activation have highlighted ways in which plants can overcome attempts to silence important RNAs in the plant. Since many genes are tightly regulated by feedback mechanisms, it is not surprising that transcriptional activation would be up-regulated in an attempt to overcome unwanted silencing of particular RNAs in the cell. The AP2 gene provides an excellent example where it compensates for undesired miRNA silencing through increased transcription to ensure sufficient AP2 protein exists within the cell (Schwab et al., 2005).

6. It is unclear how broadly susceptible insects are to off-target effects related to ingesting siRNA through their diet. It is clearly not ubiquitous as organisms of the same genus (e.g. *Caenorhabditis elegans* vs. *Caenorhabditis briggsae*) are known to have differing susceptibilities (Nuez and Félix, 2012). Thus, even when transcriptome data is available to identify possible off-target effects in these organisms, it does not indicate the organism is susceptible to the siRNAs, nor does it provide any evidence they are consumed in sufficient quantities to produce physiological effects in susceptible organisms.

Due to the many challenges associated with predicting and analyzing siRNA off-targets, many regulatory bodies have questioned the value in performing such bioinformatics analyses. During a recent European Food Safety Authority meeting on RNAi-related food safety issues, these topics were discussed in great detail with contributions from academic, regulatory, and biotech industry participants (EFSA 2014). The consensus on this topic was that one should be cautious when considering the off-target effects of a bioinformatics analysis. Instead, bioinformatics results are best used to guide the design of inverted repeat sequences. Nevertheless, we include in this report a comprehensive analysis of off-target effects based upon the most robust potato transcript databases available at MSU.

Bioinformatics-based off target prediction

Our bioinformatics method for analyzing potential off-target effects in the potato was based upon a three-step process:

1. Identify all possible siRNAs that could be derived from the dsRNA structures associated with the inverted repeats in Innate™ potatoes.

2. Identify all known potato transcripts that have complementary binding sites for any of the siRNAs.

3. The gene description for identified transcripts was determined by cross-reference with a GFF-formatted database.

In plants, dsRNA can be processed into either 21-nt or 24-nt siRNA with production of 22-nt siRNAs generated through an independent mechanism. We focused our bioinformatics analysis on the most comprehensive class, 21-nt siRNA, as this will identify the most potential off-targets, including those that would be identified through analysis of 22-nt and 24-nt siRNA.

Table 1. Potential siRNA off targets for pR1/pPhL inverted repeat identified by bioinformatics.

Transcripts	Gene Identifier / Descriptor	Sequence identity (bp)[1]	Matching siRNA[2]
PGSC0003DMT400084175	hypothetical gene of unknown function	163	143
PGSC0003DMT400007913 PGSC0003DMT400007914	Tetraspanin10	64	44
PGSC0003DMT400026560	Leucine aminopeptidase, chloroplastic	33	13
PGSC0003DMT400045411	transport protein	28	8
PGSC0003DMT400071567	Hypothetical gene of unknown function	27	7
PGSC0003DMT400056074	UDP-glucuronosyltransferase	27	7
PGSC0003DMT400030708	AG-motif binding protein-3	26	6
PGSC0003DMT400027382	Homology to unknown gene	25	5
PGSC0003DMT400076925	Oxidoreductase / transition metal ion binding protein	25	5
PGSC0003DMT400000825	Hypothetical gene of unknown function	24	4
PGSC0003DMT400048985	Hypothetical gene of unknown function	24	4
PGSC0003DMT400069580	kinase interacting protein	23	3
PGSC0003DMT400043095	Pentatricopeptide repeat-containing protein, mitochondrial	23	3
PGSC0003DMT400009611	Bel1 homeotic protein	22	2

1. Sequence identity refers to the size of the contiguous region of complementarity between the transcript and the inverted repeat (e.g. number of independent siRNA + 20).

2. Matching siRNA refers to the number of independent siRNA predicted from the inverted repeats with complementarity to the particular transcript. All listed transcripts are associated with siRNA from the pPhL/pR1 inverted repeat. None were identified for the Asn1/Ppo5 inverted repeat.

The only targets identified for the Asn1/Ppo5 inverted repeat were the *Asn1* and *Ppo5* genes,

which were targeted by design. Analysis of the pR1/pPhL inverted repeat identified 14 different genes that possessed complementarity to the potential 21-nt siRNA. The region of sequence identity between the inverted repeat and most of the identified transcripts was small compared with the hypothetical gene of unknown function and member of the tetraspanin family (Table 1).

There is no evidence of a phenotype or biochemical pathway that could be disrupted by the hypothetical gene, nor is there evidence that it serves as the source of a protein in the potato. The second gene belongs to the tetraspanin family of transmembrane proteins which are associated exclusively with eukaryotes and often duplicated in the genome. Arabidopsis contains 17 tetraspanin genes where only one, EKEKO, has been phenotypically characterized and was shown to function in leaf and root patterning during development (Wang, Vandepoele, & Van Lijsebettens, 2012). We have not observed any developmental phenotypes in our Innate™ potatoes that suggest tetraspanin10 is being silenced. If it is, the level of silencing is insufficient to produce a measurable phenotype in the host plant.

The rest of the identified targets have very limited sequence identity and are less likely to be actual off-target genes. None of them have clear biological roles that would allow us to evaluate functional silencing. Unlike our targeted phenotypes where we can measure downstream effects to know any measured silencing is biologically significant, we cannot do the same for these genes.

Conclusion

We have performed a bioinformatics analysis to identify potential transcripts that could be inadvertently silenced through off-target effects in the potato genome. The Asn1/Ppo5 inverted repeat was shown to be highly specific as we did not detect any off-targets associated with the 21nt siRNAs; whereas a small number of transcripts may be off-targets of siRNA derived from the pR1/pPhL inverted repeat. However, none of the potentially-affected genes were known to, or expected to, have biologically critical roles in the potato or measurable phenotypes. Most importantly, none of the genes identified raised any concerns regarding safety.

Experiments designed to study the effects of overexpressing miRNAs in plants have identified plants with developmental defects, such as the absence of petals, sepal transformation into carpels, uneven leaf shape, delayed flowering time, and male sterility (Achard et al., 2004; Aukerman and Sakai, 2003; Chen, 2004; Palatnik et al., 2003; Schwab et al., 2005). Agronomic line selection of Innate™ potatoes ensures only lines with normal morphological and developmental profiles are propagated to prevent phenotypes associated with off-target effects.

In summary, a bioinformatics assessment of the inverted repeats contained in the pSIM1278 plasmid used in the transformation of the Innate™ potatoes did not uncover a significant number of potential off-targets, and none of those identified were associated with pathways that suggested the potential for a safety concern. These conclusions are consistent with normal development, agronomic, and disease phenotypes of Innate™ potatoes in the field, as well as, compositional equivalence of tubers.

An analysis of potential off-target effects in organisms associated with the potato ecosystem was not possible due to limitations in transcriptome sequences. Since the siRNAs are only expressed in tubers, which are located below ground the potential for off-target effects is quite low and limited to a very small number of organisms. Our silencing constructs were not designed to target the open reading frames and therefore less likely to target sequences conserved between organisms, which further reduces the likelihood of an unexpected effect in another organism.

Methods

A Python script was used to identify all 21-nt siRNAs that could potentially arise from processing a particular inverted repeat (ASN/PPO vs. pPhL/pR1), which were deposited into FASTA-formatted files (siRNA_21mers_asn_ppo_stem.txt and siRNA_21mers_phl_r1_stem.txt). The siRNAs were compared to the current potato transcript database (56,218 sequences) available from the Michigan State University repository to identity perfect complementarity between siRNA and transcripts. An example of the search query is provided, where siRNAs is the FASTA database and pot31RNA is the transcript database:

blastn –task blastn-short –query siRNAs –db pot31RNA –out outfile.txt –outfmt 7 –perc_identity 100 –word_size 21 –strand minus

The search results were accumulated in text files and imported into MS Excel™ for evaluation. The file, "siRNA_offtargets_pSIM1278.xlsx", consists of a tab associated with each inverted repeat and the associated off-targets (expected targets removed for clarity). The last column (column M) in each data sheet was added manually by cross-referencing the subject identifier (column B) with the annotated potato database (e.g. Sequence ID Search) available from MSU (http://potato.plantbiology.msu.edu/integrated_searches.shtml) to determine the actual gene name.

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Supplement E

Safety Considerations for Nucleic Acid, including Double-Stranded RNA and siRNA

(Supplement C in response to CFIA/Health Canada questions from August 27, 2014)

Safety of Nucleic Acids

In 2001, EPA established an exemption from the requirement for a tolerance for residues of nucleic acids that are part of a PIP (40 C.F.R. 174.507) under the Federal Food, Drug, and Cosmetic Act (FFDCA), noting that "[n]ucleic acids are ubiquitous in all forms of life, have always been present in human and domestic animal food and are not known to cause any adverse health effects when consumed as part of food" (66 Fed. Reg. 37817, July 19, 2001). FDA reached a similar conclusion, stating that nucleic acids were "generally recognized as safe" for purposes of FFDCA (57 Fed Reg. 22984, 22990, May 29, 1992).

Safety of Gene Silencing Methods

Crops, including tomato, squash, soybean, papaya, potato, and plum, with traits that resulted from RNAi, have been deregulated by APHIS and CFIA and evaluated for food safety by Health Canada and the FDA. In many of these products, a small piece of RNA interferes with production of an enzyme, and thus influences a quality or nutritional trait. Innate™ potatoes contain gene silencing cassettes for *Asn1, Ppo5, R1,* and *PhL*, all of which result in small RNAs that regulate gene expression. Such small RNA (sRNA), including siRNA, miRNA, and piRNA, in plants and animals are generally involved in regulating endogenous gene expression, repressing transposons, or targeting invading pathogens for destruction. The sRNA are ubiquitous in nature, including prokaryotes where sRNA have also been associated with the antiviral CRISPR pathway (Karginov and Hannon 2010). All of these pathways rely upon an RNase III endonuclease to process a double-stranded RNA (dsRNA) precursor into small effector RNAs that can be used to target RNA or DNA for modification or destruction. Due to bacterial colonization of our intestines and our daily diets of plants, animals, and fungi expressing their own spectra of sRNA, we are constantly exposed to a multitude of sRNA.

A publication by Chen-Yu Zhang's team claimed that a plant-derived miRNA had the potential to survive substantial obstacles to elicit a biological activity in the liver of humans and mice (L. Zhang et al. 2012). The implications of these findings led to a number of studies aimed at reproducing the author's study. However, these claims have not been substantiated (Dickinson et al. 2013; Snow et al. 2013; Witwer et al. 2013; Y. Zhang et al. 2012), and have been challenged by many experts in the field leading to self-correction of the scientific literature through publication of these numerous failed replication studies (Editorial 2013). The work of Dickinson and colleagues showed the physiological effects observed by Zhang et al. were actually a result of an unbalanced diet, rather than miRNAs (Dickinson et al., 2013).

The results of the Zhang manuscript were central to the argument put forth by Jack Heinemann and colleagues in a communication calling for more rigorous safety testing of RNAi-based biotech products due to potential off-target effects of sRNA (Heinemann et al. 2013). The

concerns of Heinemann and colleagues were thoughtfully considered by fellow scientists associated with the bi-national governmental regulatory agency, Food Standards Australia New Zealand (FSANZ), which evaluates food safety requirements for biotech foods. In their formal response, FSANZ concluded, "The weight of scientific evidence published to date does not support the view that small dsRNA in foods are likely to have adverse consequences for humans" (FSANZ 2013).

The history of safe use, complexity of the human GI tract, irreproducibility of the cited controversial manuscript (L. Zhang et al. 2012), our compositional and nutritional data, and the unique characteristics of Innate™ potatoes collectively establish these potatoes as safe for human consumption. In fact, there is no scientific rationale to suggest that sRNA present in GM-foods are any less safe than those naturally abundant and safely consumed in our current diets.

Stability through Microvesicles or Protein Complexes. Another possible mechanism to increase stability of siRNA would be for the plant to package them into microvesicles (exosomes) or apoptotic bodies or bind them to large protein or lipid-protein complexes. Plants are not thought to package cellular material into apoptotic bodies or microvesicles for destruction by other cells, as is done in animals. Instead, during programmed cell death, they concomitantly shrink their protoplasm while destroying cellular contents in an effort to contain a pathogen within the original cell structure to maintain structural integrity (van Doorn et al. 2011). A large amount of programmed cell death would thus be associated with sick plants that are not included in the food production process. A recent highly-quantitative study found that there was far less than one miRNA per exosome in human samples, indicating that individual exosomes do not carry biologically significant numbers of miRNAs (Chevillet et al., 2014) and thus question their significance when detected in human tissue by highly sensitive sequencing methods (Lukasik and Zielenkiewicz, 2014). Thus, even if small numbers of siRNA/miRNA were to survive the digestive tract they are unlikely to have biological significance.

The biological activity of sRNA is linked to association with RNA induced silencing (RISC) complexes. A number of distinct cellular pathways exist in plants and animals for processing sRNA and executing their biological activities, where each pathway includes protein complexes that bind to longer dsRNA, siRNA duplexes, or the sRNA species (Pumplin and Voinnet 2013). These protein complexes are considered critical for stabilizing sRNA as unincorporated sRNA (i.e. passenger strand) are more rapidly turned over. Turchinovich and colleagues found that the vast majority (>97%) of miRNAs identified in their culture media and plasma samples were not contained within vesicles, but were instead protected from degradation by a protein involved in the RISC complex, which will not be taken up by cells (Turchinovich et al. 2011).

In summary, there is evidence that siRNA may be protected by association with RISC complexes within and outside of cells. However, since protein transport across cell membranes is highly regulated, these complexes may protect sRNA from degradation and prevent their indiscriminate uptake by human cells. The challenges of packaging sRNA have been realized by the pharmaceutical industry, which has spent considerable time and effort attempting to develop techniques aimed at optimizing the stability, delivery, distribution, and pharmokinetics of sRNA for use as orally delivered therapeutics with limited success (Castanotto and Rossi 2009; Scaggiante et al. 2011). One of the groups that rebutted the work by the Zhang group, miRagen Therapeutics, could have benefitted from confirmation of those studies.

Uptake of sRNA in Animals. While genes in some simple organisms can be targeted through feeding upon organisms expressing double-stranded RNA (dsRNA), this is highly unlikely in higher organisms, such as humans. Humans have complex GI tracts that present numerous obstacles to the uptake of dietary RNA, have many more cells to prevent non-specific accumulation, and lack components of the RNAi pathway (e.g. RNA-dependent RNA polymerases) that could amplify and sustain a non-specific response (Petrick et al. 2013). In addition to the plethora of sRNA consumed through a normal diet, humans possess trillions of microbes within their digestive tracts that can both absorb and secrete their own sRNA, which have also been detected in human plasma samples (Wang et al. 2012).

Bioactivity of plant-derived sRNA in mammalian cells. The Lam lab investigated plants as a delivery system for siRNAs that could target viruses in consumers (Zhou et al. 2004), whereas the Lee lab explored the potential of using plants as an economical factory for production of siRNA (Chau and Lee 2007). These conflicting datasets are the only mammalian studies we are aware of that address bioactivity of plant sRNA in mammalian cells, but a study was performed in the model organism, *Caenorhabditis elegans*, which is a highly-sensitive system for inducing and detecting RNA interference activity. Consistent with the results of Chau et al., they did not find biological activity of plant-derived siRNA (Boutla et al. 2002; Chau and Lee 2007). Interestingly, they were able to induce an RNAi-mediated phenotype when injecting longer dsRNA derived from plants. These results may suggest the structure of plant siRNA are inconsistent with animal systems or that exogenous siRNA are much less efficient at inducing a biological phenotype than dsRNA being processed by the cell's own machinery. It remains unclear whether the very modest phenotype reported by the Lam group is dependent upon RNAi as they were treating cells with impure samples, including longer dsRNA that may have activated a cellular immune response.

Processing of dsRNA from inverted repeats in plants can produce multiple classes of sRNA, including 21-22 nt and 24 nt species. The 24 nucleotide population is especially unlikely to have RNAi activity in animals as they are not involved in degradation of target transcripts even in plants (Fusaro et al. 2006).

Summary of RNAi safety. In summary, humans consist of cells, tissues, and organs that remain homeostatic in the presence of varying diets consisting of abundant sRNA. It is highly unlikely that a sufficient quantity of these sRNA would survive the GI tract and accumulate in a given human cell resulting in a short-term, let alone a long-term, biological effect. In addition, the human body possesses a number of immune regulatory pathways dedicated to specifically detecting and destroying exogenous dsRNA as a means of protecting against foreign invaders.

Scientific rationale of the safety of orally ingested siRNA(s) derived from Innate™ potatoes. As described previously, the scientific literature does not support a model whereby sRNA present in consumed food pose a safety risk to humans following consumption (Petrick et al. 2013). In contrast there is a long record of safe consumption of sRNA within our natural diet. There are a number of important characteristics of our Innate™ potatoes and their use of RNAi:

- The Innate™ potatoes rely upon potato genomic DNA to initiate gene silencing using the plant's endogenous pathway. The inverted repeat sequence is derived from the sequence of the genes that are already being expressed in the potato.

- Many common potato preparation or cooking practices involve heating at high temperatures, which result in the conversion of asparagine with sugar into acrylamide, which has been associated with health concerns (Health Canada 2013). Innate™ potatoes use RNAi to reduce the accumulation of the precursor asparagine to limit acrylamide potential. Thus, Innate™ potatoes provide a consumer product with potentially enhanced safety.

- Processing of potatoes by consumers or the food industry involves treatments that are likely to limit the amount of sRNA in the final product. In addition to high temperature heating, treatments such as blanching, frying, dehydration, and freezing are commonly used, which lead to degradation and fragmentation of double-stranded genomic DNA. A similar fate is expected for sRNA as was shown in processed milk (Chen et al. 2010).

- The Innate™ potatoes under consideration do not target an evolutionarily conserved exogenous animal gene as might be the case when RNAi is used as a plant incorporated protectant. Since RNAi in Innate™ potatoes exclusively target plant genes, they are less likely to have adverse off-target effects in animals.

- We have performed rigorous compositional, nutritional, and agronomic analyses and have not observed any evidence of off-target effects in the plant where expression of sRNA was the highest and the potential for off-target effects greatest.

Numerous physiological barriers have impeded introduction of nucleic acid through oral uptake (O'Neill et al. 2011), and as noted previously, there is a long history of safe use associated with eating foods containing sRNA due to its ubiquitous presence in nature (Ivashuta et al. 2009; Jensen et al. 2013; Petrick et al. 2013). Mechanistic studies of a number of cultivars have shown plants selected for agronomic traits using conventional breeding techniques are using RNAi to silence their own genes through expression of inverted repeats (Della Vedova et al. 2005; Kusaba et al. 2003; Tuteja et al. 2004).

Comments presented to the EPA's Scientific Advisory Panel Public Meeting on RNAi technology as a pesticide, held January 28, 2014, included support for the safety of dsRNA by experts in the field (Mello 2014). Dr. Mello reported that oral uptake of dsRNA has proven unfeasible as a drug delivery route, thus unlikely to cause off-target effects when used for gene silencing in plants. He also reported that ingested RNA is rapidly metabolized in the gut where it is converted to nutrients, thus proposing that bioinformatics testing for similar sequences in humans would be unnecessary. Also, RNA is digested rapidly, suggesting that digestibility assays would be unnecessary for dsRNA.

In summary, we believe the history of safe use, the irreproducibility of the cited controversial manuscript (L. Zhang et al.2012), the submitted compositional and nutritional data, and the unique characteristics of Innate™ potatoes collectively establish these potatoes as safe for human consumption.

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Supplement F

Bioinformatics Analysis of Inserts

(Supplement E in response to CFIA/Health Canada questions from August 27, 2014)

The transformation process that introduces DNA into the genome of the potato has the remote potential to disrupt a native gene or introduce an unexpected toxin or allergen through expression of a novel open reading frame (ORF). This report describes our analysis of possible native gene disruption, toxicity, and allergenicity for four Innate™ potato events using the standard bioinformatics techniques summarized in Table 1.

Disruption of native genes and expression of unexpected toxins or allergens are all highly unlikely events, particularly in Innate™ potatoes that rely almost exclusively upon native potato DNA. In addition to promoter and enhancer elements, expression of unexpected proteins would require productive transcription through the insertion region with post-transcriptional processing producing a properly structured and polyadenylated messenger RNA transcript, followed by translation into a stable protein. Innate™ potato constructs include inverted repeats driven by opposing promoters, which limit transcriptional read through from either direction. The end result, by design, is small complementary RNAs or double-stranded hairpins that are processed by the RNA interference pathway into small interfering RNAs, preventing them from being translated. Nonetheless, we show the absence of allergenicity and toxicity potential of our events using a number of well-established bioinformatics techniques (Ladics, 2007; Goodman, 2008; Terrat, 2013).

Table 1: Overview of bioinformatics analyses

Analysis	Purpose	Approach
Stop-to-stop ORF Analysis	Identify all potential proteins that may be expressed by DNA insert and surrounding sequence.	ORF Finder: systematically identify all ORFs (≥20 amino acids) located between contiguous stop codons from all frames. Used for subsequent toxin and allergen analyses.
Allergenicity Analysis	Ensure that sequences capable of expressing known allergens have not been introduced by transformation.	AllergenOnline: find small regions of identity (8 amino acids) or larger regions of similarity (80 amino acid, ≥35% homology) with known allergens.
Toxicity Analysis	Ensure sequences capable of producing proteins similar to known toxins have not been introduced by transformation.	NCBI protein BLAST (blastp): identify proteins homologous to known toxins contained in target databases (E-value ≤ 1).
Native gene disruption	Verify that a novel protein has not been generated by integration within a native gene.	NCBI nucleotide BLAST (blastn): identify any native genes containing the flanking sequence as an indication of gene disruption.

RESULTS

Stop-to-stop ORF identification

Open reading frames (ORFs) can be identified as the contiguous sequence located between a canonical start codon and a downstream stop codon or, more generally, all sequence located between two stop codons in the same reading frame. As the latter definition will identify more ORFs, we used it as the basis for our analysis. The ORF Finder algorithm associated with the Sequence Manipulation Suite (Stothard, 2000) was used to identify all ORFs. As shown in Figure 1, the analysis of each event was performed using each insert with the known flanking sequences. The ORFs overlapping the known junction sites were included within each analysis. In total, each analysis spanned a region consisting of at least 11 kb of nucleic acid sequence for each event.

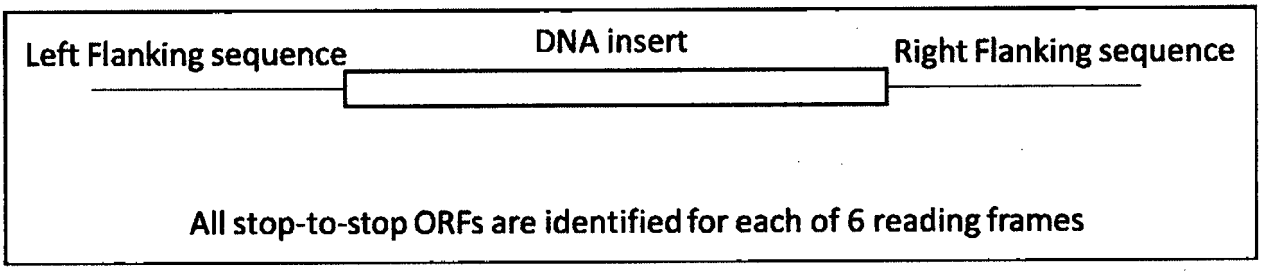


Figure 1. ORF Analysis Scheme

As many of the identified ORFs are replicates due to the redundant nature of the sequence contained within the DNA insert, the dataset was trimmed to only include unique ORF sequences. These ORFs were converted into a FASTA-formatted file and used for the subsequent toxicity and allergenicity analyses. As summarized in Table 2, we identified between 232 and 310 unique ORFs for the events.

Table 2 - Stop to Stop ORF Analysis Summary

Event	Number of ORFs	Mean ORF size (amino acids)	Largest ORF size (amino acids)
E12	232	37	182
F10	239	38	182
J55	289	36	182
J3	310	38	182

Allergenicity evaluation

The allergenicity potential of these ORFs (Table 2) was analyzed using a web-based tool (http://www.allergenonline.org/databasefasta.shtml) provided by the Food Allergy Research and Resource Program (FARRP). This tool allowed us to identify small regions (8-mers) of sequence identity between the ORFs found in each of the events and those of known allergens. These eight-amino acid matches could theoretically represent a B-cell or T-cell epitope, which is the part of the protein that is specifically recognized by the immune system (Metcalfe, 1996). The allergen database contains the sequence of known allergens, but the specific sequence responsible for allergenicity is not necessarily known, nor is it known whether an 8-mer is capable of inducing an allergic response (Goodman, 2008).

8-mer identity search

As shown in Table 3, a FASTA search led to identification of a single match between all events and a known allergen, endochitinase (GI:3201547) from *Persea Americana* (avocado). There were two independent ORFs containing this sequence within our construct because the open reading frame is contained within the GBS promoter native to the potato, which was coopted to drive expression of the silencing constructs contained in the insert. This polypeptide represents one of 319 distinct 8-mers in the full-length allergenic endochitinase protein, which makes it unlikely this particular 8-mer is responsible for the allergenicity. Further support is provided by the absence of the putative epitope from a database of known epitopes (http://www.iedb.org/). IgE cross reactivity has been observed between the endochitinase protein from avocado and latex proteins sharing a prohevein domain (Sowka, 1998). This particular domain does not include the N-terminal region containing the 8 amino acid, LPLLLLLL, motif identified in our search, which provides further evidence that this motif does not have known allergenic potential.

The presence of an ORF does not predict that it will be expressed, but if expressed it is not novel as the peptide sequence is present in many potato and human proteins. Collectively, these data suggest the peptide identified is a false positive and would not be a potential allergen, consistent with concerns over the high false-positive rate when looking for 8-mer matches (Goodman, 2008).

Table 3. Summary of Allergenicity Findings

Event	80-mer hits	8-mer hits	8-mer sequence	8-mer allergen target
E12	0	1	LPLLLLLL	endochitinase (GI:3201547)
F10	0	1	LPLLLLLL	endochitinase (GI:3201547)
J55	0	1	LPLLLLLL	endochitinase (GI:3201547)
J3	0	1	LPLLLLLL	endochitinase (GI:3201547)

80-mer homology search

A second analysis performed using the FARRP web-tool identifies larger regions of similarity between the ORFs and known allergens. This analysis compares all 80 amino acid sequences within an ORF and identifies any matches with greater than 35% homology to known allergens. The algorithm did not identify any potential allergens arising from ORFs found in any of the events or their flanking sequences (Table 3). Overall, no allergen-related safety concerns were identified for any of the Innate™ potato events.

Toxicity evaluation

Unlike with allergenicity studies, we are not aware of a formal method for establishing toxin-related safety in genetically-modified organisms, so we modeled our analysis after the rigorous approach used for the allergenicity studies. We consulted with experts at the National Center for Biotechnology Information (NCBI) and Uniprot to develop methods to generate and search toxin-specific databases for homology between our ORFs and known protein toxins. We took advantage of two repositories of annotated toxins for this analysis. The first database (mvirDB) consists of known bacterial toxins, virulence factors, and antibiotic resistance genes, which is a publicly-available repository maintained as a combination of at least eight independent database sources (Zhou, 2006). A second BLAST-compatible database was created to supplement the bacterial toxin database by extracting all eukaryotic proteins annotated as toxins within the Uniprot repository. These smaller and more specific databases make toxicity assessment more straightforward than non-specific searches against NCBI databases.

Table 4. Summary of Toxicity Database Queries

Event	mvirDB	uniprotToxin	NCBI nr
E12	0	0	1417
F10	0	0	2234
J55	0	0	2039
J3	0	0	2214

Using the blastp algorithm within the BLAST suite of applications available through NCBI, we analysed all of our ORFs against the NCBI non-redundant protein database (Table 4). Since the vast majority of the ORFs were small (35 amino acid average), many non-specific hits were generated making it a challenge to objectively assess toxicity although, as expected, most matches (E-value ≤ 1.0) were of potato origin. However, the blastp algorithm did not identify any proteins with significant homology when the more specific toxin databases were queried with the ORF sequences. Based on weak specificity, the potato origin of most matches within the NCBI database, and the lack of homology with the toxin database, no toxin-related safety concerns were identified for any of the Innate™ potato events.

Native gene disruption

The potato (*Solanum tuberosum*) genome presents some unique challenges for analysis of native gene disruption. Most potato cultivars are tetraploid, highly heterozygous, and include a significant amount of redundant/homologous DNA. These challenges have prevented the research community from sequencing the genome of these cultivars directly. Instead, they sequenced a unique homozygous form of the potato, a doubled monoploid, derived using tissue culture techniques (The Potato Genome Sequencing Consortium). This sequence was later used to integrate sequence from a heterozygous diploid line. Together, these efforts have provided a genome sequence that is valuable for investigating the evolution and genome organization of potatoes, but is still lacking for detailed analysis of individual loci in commercial cultivars, which are mostly tetraploid. It is not uncommon with BLAST to analyse known sequences against the current potato genome only to identify numerous hits scattered across chromosomes, or more perplexing, to retrieve no hits at all.

It is highly unlikely that a gene disruption would have a functional impact on the plant or tuber due to its tetraploid nature, which means that a single gene disruption would leave the plant with up to three functional copies of the native gene. These traits highlight the power of using biotechnology in potatoes as native gene disruptions are both uncommon and unlikely to result as a measurable or observable change in phenotype. In the event that a native gene is disrupted by an Innate™ construct, it is generally going to produce a truncated version of the native protein as opposed to a novel fusion protein since the ORFs contained in the construct are extremely short on average and would halt translation.

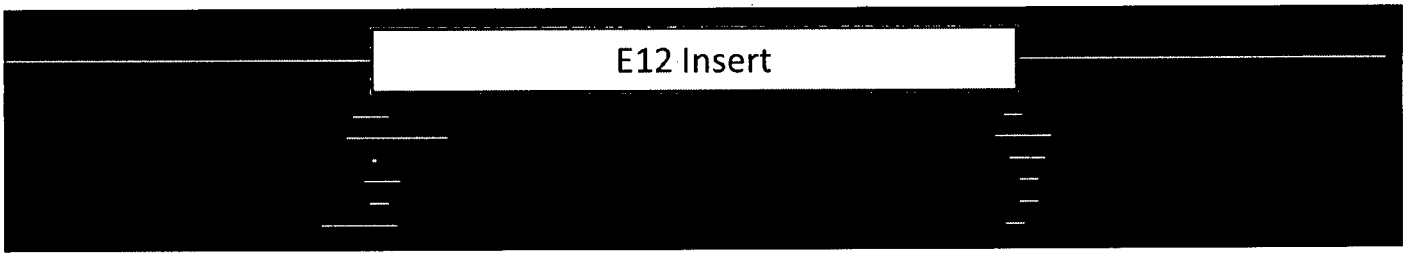
In an effort to identify the insertion site of the construct, we performed a BLAST (blastn) search against the NCBI and MSU potato genome databases to identify the likely insertion location and any annotated genes that may have been disrupted. When possible, the locus was further evaluated using the graphical viewers made available by NCBI and MSU to visually inspect the locus for disrupted genes. We also performed BLAST (blastx) searches, which translates the input nucleic acid sequences in all six reading frames and searches for protein matches. The results for each event are summarized below.

E12 Event

Despite many sequence matches, the most likely integration site appears to be on chromosome 12 (Figure 2). There is strong homology between the right and left flanking sequences identified with a locus on chromosome 12 (left flank, 56535700-56536479:56533662-56534963, right flank) according to the Michigan State University (MSU) genome database.

Neither the blastn nor blastx searches against the NCBI database identified annotated genes disrupted by the flanking sequences. A BLAST search against the "PGSC *S. tuberosum* group Phureja DM1-3 Transcripts (v3.4)" dataset revealed similarity to an expressed transcript, but that transcript maps to a different chromosome (chromosome 11) than the likely integration site (chromosome 12). Visual inspection of the tracks covering the locus on chromosome 12 using the MSU graphical genome browser did not identify any candidates for native gene disruption.

Figure 2. E12 insertion and junction open reading frames on chromosome 12



The open reading frames covering the junctions between the insert and the flanking sequences are shown in Figure 2 (not to scale). The sequences for the left (L1-L6) and right junction (R1-R6) open reading frames were analyzed and the results summarized in Table 5. No known toxins or allergens were associated with the ORFs covering the insert.

Table 5. Summary of toxicity and allergenicity analysis of ORFs at E12 insert junctions

Frame	ORF sequences	Toxins	Allergens
L1	CNNKFYIGENN**KRSVCG***	None	None
L2	ISTLSFIFTKFNVIINFILVRII**NEVCVVDPKSIVPLESVAMKDSLTYE ELPIEILDRQVRRLRKIEVASVTALWRSKGTKCLRQPKLKVGNQ TLSQRLYIQNGINIII***	None	None
L3	**	None	None
L4	**RYDRFWINHTHFVY**YSHQYKIYYYIKFGEYK*	None	None
L5	**ILDQPHTLRL**LFSPI*	None	None
L6	**VRLSFIATLSKGTIDFGSTTHTSF**IILTNIKFIITLNLVNINDRVEIHLV NINKNEGSNTFLIFHNKKKRLNLMTKHNIDKRQFSLAVPHFLNLSI RKMFVHMTEEYQVQLIEDLGKI*	None	None
R1	**ALYRVGLRSVTL**Y*	None	None
R2	**IIISGAHRYAINFIYLVGSRLYTELDYGQSL**CTSKDLFLSILSSYIKSF KEILRVREWKKHVNSE*	None	None
R3	**LGVGFIPSWTTVSHF**VLVKICFYPFYLLISNHSRKY*	None	None
R4	EDKMDKNRSLLV**QSD***	None	None
R5	KQIFTST**K***	None	None
R6	Y**KVTDRSPTRYKAYSQLNI***	None	None

- Open reading frames are shown for all junctions. Bold sequence refers to insert DNA and non-bolded sequence is plant.

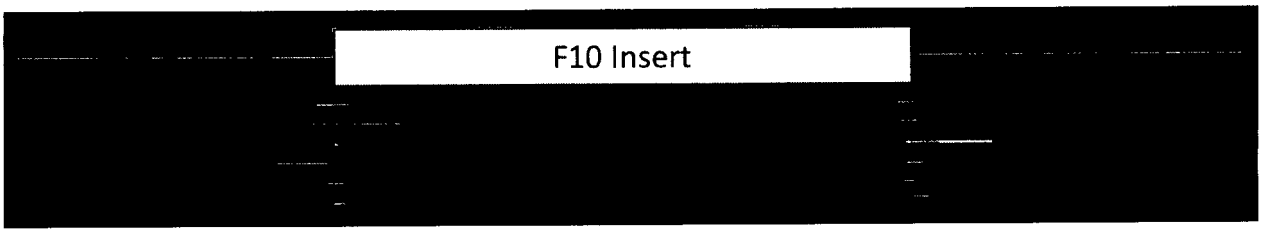
Since there is no evidence of a native gene disruption, no known allergens or toxins associated with the ORFs, and no unexpected differences in composition or agronomy, there is no evidence of a safety concern with E12.

F10 Event

As with the E12 event, both the left and right flanking sequences were determined for the F10 insert. Although there are numerous high quality matches using the MSU potato database, the most likely integration site is on chromosome 8 (left flank, 49751958-49752732:49750820-49751488, right flank).

When a BLAST search is performed against the transcripts cloned from potato, there is similarity to a transcript, PGSC0003DMT400045203, which is annotated as a putative gene. Although it is possible that a native potato gene has been disrupted by the F10 insertion, we did not find any evidence that this pseudogene actually encodes a functional protein.

Figure 3. F10 insertion and junction open reading frames on chromosome 8



The open reading frames covering the junctions between the insert and the flanking sequences are shown in Figure 3 (not to scale). The sequences for the left (L1-L6) and right junction (R1-R6) open reading frames were analyzed and the findings summarized in Table 6. No known toxins or allergens were associated with the ORFs at the insert site.

Table 6. Summary of toxicity and allergenicity analysis of ORFs at F10 insert junctions

Frame	ORF sequences	Toxins	Allergens
L1	SYNNNWSSSHQLVQ**QDIYRCKRSVCG**	None	None
L2	ATLVKDEAITITGPAAISWSS**RIYTGVNEVCVVDPKSIVPLESVA MKDSLTYEELPIEILDRQVRRLRKIEVASVTALWRSKGTKCLRQP KLKVGNQTLSQRLYIQNGINIII***	None	None
L3	LVQQPSTGPAGYIP**V***	None	None
L4	**VRLSFIATLSKGTIDFGSTTHTSFTPVYI**LLDQLMAAGPVIVIASSF TNVAYERLPLEEDGNTQGSDGGGDGVVNNNPFSDPSNDGLPFF NLPLNMPNCFNPGSASVDGWVGNPSLRPPFGV*	None	None
L5	**RYDRFWINHTHFVYTGIYP**AGPVDGCWTSYCYSFIFY*	None	None
L6	**ILDQPHTLRLHRYIS**CWTS*	None	None
R1	**LGINLVHQPKI***	None	None
R2	**VISLLCGHQFS**WASI*	None	None
R3	**VSSVGINLV**GHQFSPPAKNIVKLVAPGGAGGGKNEPLSDKISNR PFNVTTDEELILPVLLLLPVLVGCLILTLVTIPLPLNIQIPRCLRLAYD DIHSNTSHPLPISRICARNVFALSLVIITGGFGLFLDPGGRPLGLRP TRSPGPDEFAPTRSN*	None	None
R4	IDAQ**LN***	None	None
R5	CP**TKLMPTEETYNLQGHVVLGLESD***	None	None
R6	WFVFTTTSTTRGNKFDYIFGWWTKLMP**N***	None	None

- Open reading frames are shown for all junctions. Bold sequence refers to insert DNA and non-bolded sequence is plant.

Since these potatoes are tetraploid, the F10 potato has three unmodified copies of the putative gene so a disruption is unlikely to have an effect on the potato itself. The compositional and agronomic data were consistent with this conclusion as the only measurable differences

between the F10 event and its commercial parent were those targeted by the gene silencing cassette. Since the bioinformatics analysis did not find any evidence of a potential toxin or allergen created by the insertion, there is no evidence of a safety concern associated with the putative gene disruptions in F10.

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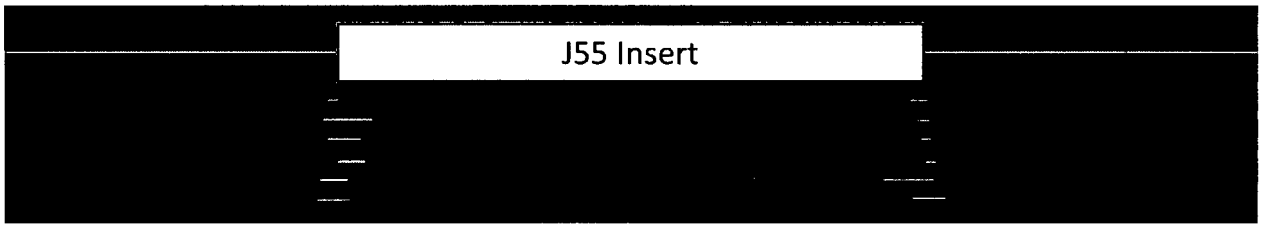
J55 Event

Unlike with the other events, there were very few matches between the J55 flanking regions and the potato genome when analyzed using MSU's potato database as there are major sequence differences between the published sequence and Atlantic varieties. The search results suggest the insertion integrated on chromosome 4 (left flank,9547964-9549110:9549165-9550321, right flank). Similar to F10, this integration appears to fall within a gene of unknown function (PGSC0003DMG400027260).

Figure 4. J55 insertion and junction open reading frames on chromosome 4



The open reading frames covering the junctions between the insert and the flanking sequences are shown in Figure 4 (not to scale). The sequences for the left (L1-L6) and right junction (R1-R6) open reading frames were analyzed as described above and are summarized in Table 7. No known toxins or allergens were associated with the ORFs covering the insert.

Table 7. Summary of toxicity and allergenicity analysis of ORFs at J55 insert junctions

Frame	ORF sequences	Toxins	Allergens
L1	KSTSN*	None	None
L2	LVFSRRIWTENQQAI**EELPIEILDRQVRRLRKIEVASVTALWRSK GTKCLRQPKLKVGNQTLSQRLYIQNGINIII***	None	None
L3	SNSQLESNLSFPEEFGLKINKQL**KNYLLRFLIVRSEG***	None	None
L4	**RSRISIGSS**SIAC*	None	None
L5	**FF**NCLLIFSPNSSGKDKLDSS*	None	None
L6	**VVL**QLLVDFQSKFFWKRQVRF*	None	None
R1	**VRL**CVKLSGCFSDMTQLP*	None	None
R2	**FFISET**MRETFRLLLRYDTTTLRSSF*	None	None
R3	**DY**A*	None	None
R4	KFHA*	None	None
R5	PQGSCVISEKQPESFTH**SLTYEELPIEILDRQVRRLRKIEVASVTAL WRSKGTKCLRQPKLKVGNQTLSQRLYIQNGINIII***	None	None
R6	YMKNSSFTYQKDDLKVVVSYLRSNLKVSRI**VSLMKNYLLRFLIVRS EG***	None	None

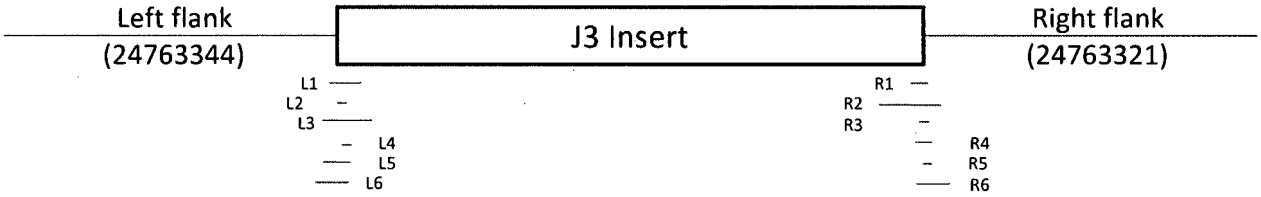
- Open reading frames are shown for all junctions. Bold sequence refers to insert DNA and non-bolded sequence is plant.

Since this tetraploid event contains three unmodified copies of the disrupted gene, no allergens or toxins are associated with the ORFs, and no unexpected differences in composition or agronomy were identified, there is no evidence of a safety concern with J55.

J3 Event

According to the MSU genome browser, the chromosomal insertion site was 862 bp upstream of a putative gene/transcript of unknown function (PGSC0003DMT400095935) on chromosome 6. Protein BLASTs against the NIH database did not reveal any likely protein functions for the 128 amino acid, putative polypeptide encoded by this transcript. As the insert did not disrupt the transcript, it would not result in a novel fusion protein or a modified version of the native protein. Furthermore, BLASTs against the MSU transcript database did not identify any evidence of other transcripts derived from this locus that could be disrupted.

Figure 5. J3 insertion and junction open reading frames on chromosome 6



The open reading frames covering the junctions between the insert and the flanking sequences are shown in Figure 5 (not to scale). The sequences for the left (L1-L6) and right junction (R1-R6) open reading frames were analyzed and the results summarized in Table 8. No known toxins or allergens were associated with the ORFs at the insert site.

Table 8. Summary of toxicity and allergenicity of ORFs at J3 insert junctions

Frame	ORF sequences	Toxins	Allergens
L1	PHIYFCSIISSIRVIDIDQNRYSNLQQDNHKL**GNSHAMK***	None	None
L2	***ETHML***	None	None
L3	SKPVLKFATGQPQAR**KLTCYEINSHLTTP***	None	None
L4	***SV***	None	None
L5	*RYQDFGTSLNAVPCGCAL**FSVH**	None	None
L6	*FRYEFKCCSLWLSP**FECAIFYI**	None	None
R1	*KSPR**INFFWKGQKSFTIKSKEPQAQASTKAV**	None	None
R2	*FDEKALEL**IFFGRVKNHLQLKARSHKLKHPQKQCKNTIFS LKPKYKQNRNYEYRTKGEPHPTTNKSNLSSNANKNIIYTS QNKSKTGRELKRGSCLRSRSIFLGISARCISLDLGISAVHLSG LGPQYLGSPQKEQHYQTH**	None	None
R3	***FFLEGSKIIYN***	None	None
R4	*MQKIFFAKFKLKEPQNSSFARSN**IKKPLTLF**	None	None
R5	***NKKSPDFIM**	None	None
R6	*NSIKKQRNSELPKFNSNKCKNSSFPRLNSNKRNIQHFLGLI LKKQFP	None	None

- Open reading frames are shown for all junctions. Bold sequence refers to insert DNA and non-bolded sequence is plant.

Since the insert did not disrupt a gene, no allergens or toxins are associated with the ORFs at the junctions, and no unexpected differences in composition or agronomy were observed, there is no evidence of a safety concern for J3.

MATERIALS AND METHODS

ORF detection

All potential open reading frames (ORFs) created as a result of the event-specific, integration event were identified using the ORF Finder web application (Stothard, 2000) available through the Sequence Manipulation Suite (http://www.bioinformatics.org/sms2/orf_find.html). The search parameters were defined to identify all ORFs with at least 20 amino acids located between two contiguous stop codons. A nucleotide sequence has the potential to be translated in up to three reading frames consisting of contiguous codon triplets from RNA transcribed from either direction on the chromosome. All six open reading frames were analyzed to identify ORFs using the insert sequence and flanking plant genomic sequence on each side. The 500 nucleotides of flanking sequence is more than enough to account for any potential ORFs encompassing the junction sequences. The results were converted into FASTA-formatted files for further analysis.

Database and software resources

The most recent Blast software suite (v2.2.28; Altschul, 1997) was downloaded from NCBI (ftp://ftp.ncbi.nlm.nih.gov/blast/executables/blast+/LATEST/) and installed locally. A number of BLAST-compatible databases were generated and/or downloaded to support the toxin analysis described herein. The most recent NCBI non-redundant (nr) protein database (August 26, 2013 post date) was downloaded using the update_blastdb.pl script provided with the BLAST application suite. Searches against this database are comprehensive, but non-specific and produce data that can be challenging to associate with putative toxins. In order to perform more directed searches, we took advantage of two toxin-specific resources. The first is a microbial database of toxins, virulence factors, and antibiotic resistance genes (Zhou et al., 2006) that was downloaded from the Lawrence Livermore National Laboratory Virulence Database Home Page (http://mvirdb.llnl.gov/) and installed locally (mvirdb). This database comprises known microbial protein toxins from numerous publically available sources, including Tox-Prot, SCORPION, PRINTS, VFDB, TVFac, ARGO, and VIDA. A second eukaryote-specific (taxid: 2759) toxin database was generated by downloading all FASTA-formatted sequences annotated with the keyword=toxin from the uniprot database using a browser script provided by Uniprot technical support at the SIB Swiss Institute of Bioinformatics:

http://www.uniprot.org/uniprot/?query=taxonomy%3a2759+keyword%3atoxin&force=yes&format=fasta&include=yes

This toxin dataset was converted into a BLAST-compatible database (uniprot_toxin) using the makeblastdb.exe utility provided in the BLAST software suite.

Allergenicity database searches

Allergenicity potential was evaluated using the public, allergen-specific search engine (http://www.allergenonline.org/databasefasta.shtml) available through the Food Allergy Research and Resource Program at the University of Nebraska. The ORFs associated with the insert and flanking regions were analyzed using two approaches: (1) 80-mer sliding region homology search and (2) 8-mer identity search. Only protein sequences consisting of 28 or more amino acids were analyzed using the 80-mer sliding window as this is the minimum sequence size capable of reaching the lower threshold target of 35% homology. However, all ORFs were analyzed using the 8-mer match. All searches were performed using database version 13, dated February 12, 2013.

Toxin database searches

The comprehensive set of ORFs predicted by the ORF Finder application was used as input for BLAST (blastp) searches against the databases described above. When performing blastp searches it is common to consider the Expect value (E-value) as a measure of statistical significance where values less than 0.1 or 0.05 are generally considered biologically significant (BLAST help). That is, the E-value describes the number of hits that one might "expect" to see by chance when searching a database of a particular size. In order to consider any potential homology between the ORFs and the sequences in the toxin-specific databases, we analyzed our BLAST searches using a higher E-value threshold of 1.0. However, since the E-value calculation is dependent upon the size of the search space, we consulted with a BLAST application expert at NCBI to determine the appropriate search space (–searchsp) parameter for our toxin database searches. BLAST reported an effective search space of roughly 1×10^{11} when the ORFs were compared to (blastp-short) the NCBI nr database. Thus, our database searches used the following command line input:

>blastp –task blastp-short –query ORFs.fa –db database –out db_output.txt –searchsp 100000000000 –outfmt 6 –evalue 1.01

The *database* string was replaced by nr, mvirdb, or uniprot_toxin depending on the specific search. The nr searches served as a control to ensure our searches were performing as expected. The algorithm applies the PAM30 scoring matrix with gap penalties of 9 for existence and 1 for extension as a default associated with the blastp-short search parameter.

Native gene disruption

Where available, the sequences identified as the left and right flanking regions were used as input for a BLAST (blastn) search against the NCBI potato genome to identify the likely integration site and any genes associated with the flanking regions (E-value cutoff of 1×10^{-6}). The same sequences were used to search the more frequently updated potato genome housed at Michigan State University (MSU) (http://potato.plantbiology.msu.edu/integrated_searches.shtml). All searches were performed against the most recent version of the database (v 4.03). The sequences were also provided as input for BLAST (blastx) searches to identify any homologous proteins to the nucleotide coding sequence. This algorithm compares the translational products of the nucleotide sequence from all six reading frames to proteins in the database. These searches were also performed against

the NCBI potato database (E-value cutoff of 0.01).

CONCLUSIONS

Using a number of well-established bioinformatics tools, we have performed a comprehensive analysis on the insert and flanking regions of the Innate™ potato events: E12, F10, J55 and J3.

Although F10 and J55 are predicted to have inserts disrupting a putative native gene according to genome annotation, each of these lines is derived from a commercial tetraploid variety. Thus, each of these events contains three unmodified copies of the native genes and exhibit no unexpected differences in agronomy or molecular composition. Furthermore, neither the allergenicity nor toxicity analyses uncovered any potential safety concerns associated with any of these events, including the junction regions. This is not surprising considering the source of the DNA used in the Innate™ potato events is almost exclusively derived from the host, potato.

Collectively, our bioinformatics studies did not identify any safety concerns associated with any of the events as a result of the transformation.

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BLAST help:
http://blast.ncbi.nlm.nih.gov/Blast.cgi?CMD=Web&PAGE_TYPE=BlastDocs&DOC_TYPE=ProgSelectionGuide

s.21(1)(a)

s.21(1)(b)

From: Nataliya Dormann
To: "philip.macdonald@inspection.gc.ca".API.EMSSCONN; Van Neste, Erika
CC: Shearer, Heather
Date: 2015-03-05 8:35 AM
Subject: Re: For your review/comment: Briefing material on regulation of products next-gen molecular techniques
Attachments: CFIA_ACIA - #6413376 - v1 - PBO comments - The regulation of new and emerging crop development technologies.DOCX

Hi Erika,
Thanks for the opportunity to review the memo and the table.
(I have checked the Memo as it describes the Canadian position, and have no comments).

Heather and I have concentrated mostly on the table, since it is more technical.

Other suggestions are attached.

>>> Van Neste, Erika 2015-03-04 10:11 AM >>>
Good morning Phil and Nataliya,

I was hoping that someone from your respective groups would be able to take a quick look at the attached analysis, which does a (very surface level) comparison between Canada, the U.S., and the EU concerning how crop products of next-gen non-GE molecular techniques for crop improvement (such as nuclease-based gene editing) would be regulated in these jurisdictions. This issue has been raised in a number of joint briefings we have had with STB in the last several months, including in a briefing with the DM in December where she made the request for this analysis to be done.

The goal of the attached memo is to present our analysis thus far to our STB colleagues, and secure their support in bringing this item forward for a general discussion at AAFC's Policy and Programs Management Committee. Depending on the direction from that Committee, there may be an opportunity to collaborate on a more fulsome analysis and/or to address some more specific questions. At this point, however, we're just looking to do a signal check that nothing we've proposed in the attached is wildly off base or problematic.

As ever, our timelines are rather tight - would it be possible to get back to me by end of day tomorrow with any thoughts or concerns? I apologize for the short window.

If you have any questions, or if there's anything I can do to make this easier or more clear, please don't hesitate to let me know.

Thanks so much,

Erika Van Neste
Policy Analyst | Analyste des politiques

Innovation and Growth Policy Division | Division des politiques sur l'innovation et la croissance
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s.21(1)(a)
s.21(1)(b)

THE REGULATION OF NEW AND EMERGING CROP DEVELOPMENT TECHNOLOGIES FOR ENVIRONMENTAL RELEASE

Below is a comparison of how crops developed using various non-GE next-generation molecular techniques would be considered for environmental release under the regulatory systems of Canada, the U.S. and the EU. The first entry in the chart below describes the regulatory trigger used to determine whether products developed using a given technique are subject to regulation in the specified jurisdiction.

Current Regulatory System Coverage of New and Emerging Crop Development Techniques in the European Union (EU),United States of America (USA), and Canada			
	EU (AAFC interpretation of the regulations) EC has been working on the issue for several years, but no position had been yet communicated	**USA**	**Canada**
Regulatory Trigger	*Process*-based Regulatory Trigger Annex IA Part 1 of Directive 2001/18/EC provides a list of techniques that lead to genetic modification. Techniques not considered to result in genetic modification are excluded from the scope of GMO legislation and are also listed	*Product*-based regulatory trigger with some consideration given to processes used in development[1]. USDA-APHIS does not regulate new breeding technologies in and of themselves; rather, its regulatory authority is limited to plants that are plant pests, were created with plant pests, or used a plant pest in the method of creation (as per 7 Code of Federal Regulations (CFR) part 340, which were promulgated pursuant to authority granted by the Plant Protection Act.) When plant pests are used, the product sponsor must first petition APHIS for a "determination of non-regulated states" before the product can be freely transported and commercialized*	*Product*-based regulatory trigger Plants with novel traits – any plant which has a new trait, not present ~~or previously characterized~~ among existing crop systems, are subject to regulation irrespective of the process by which that novel trait was introduced. If a plant was developed using genetic engineering but is not expressing a novel trait, that plant is ~~exempt~~ would not be considered a ~~from~~ PNT ~~regulation, and is regulated as a conventional~~ plant
	EU	**USA**	**Canada**
Oligonucleotide Directed Mutagenesis (ODM) Oligonucleotides target homologous DNA and induce site-specific nucleotide substitutions, insertions, or deletions through repair mechanisms. Oligonucleotides consist of DNA and	Not regulated in the EU. Products created through ODM do not meet the EU definition of transgenic and are therefore excluded from GMO legislation by Annex IB (2001/18/EC) and Annex II Part A (2009/41/EC).	Not regulated in the U.S. Products created through ODM do not meet the definition of a regulated article as defined in USDA-APHIS regulations. Therefore, a "determination of non-regulated status" is not	Regulated in Canada if they express a novel trait. Plants modified by ODM (as well as other mutagenesis techniques), if they express a novel trait, would be regulated as a PNT.

Comment [ND1]:

Comment [ND2]: Exemption is different from being out of scope (e.g. PNTs in containment are exempt from our oversight).

Comment [ND3]: conventional breeding can result in PNTs ☺

[1] USDA-APHIS takes the position that it can designate an entire plant as a regulated article, even if it was not developed using plant pests, if the plant is a product of genetic engineering and the agency determines or has reason to believe it is a plant pest.

RNA bases, and single stranded DNA oligonucleotides can be deployed for ODM in plants.		required before products containing the plant can be freely transported and commercialized*	
	EU	**USA**	**Canada**
Cisgenesis/Intragenesis A DNA sequence from the species itself or from a cross compatible species is inserted into the plant genome. In the case of cisgenesis, the inserted gene is unchanged with its own introns and regulatory sequences. In the case of intragenesis, the inserted DNA can be a new combination of DNA fragments from the species itself or from a cross compatible species. Functionally, this is the same as transgenesis (GE), but using genes from within the same species or a closely related (e.g. cross compatible) species	Regulated in the EU. Products created through cisgenesis/intragenesis meet the EU definition of transgenic and therefore are within the scope of GMO legislation by Annex IA Part 1 (2001/18/EC)	Regulated in the U.S. only when a plant pest is involved in transformation. According to USDA-APHIS responses to breeder inquiries, plants developed using cisgenic/transgenic techniques are only considered regulated articles when genetically engineered from a donor organism, recipient organism, or vector/vector agent recognized in regulation as being a plant pest or unclassified organism and/or an organism whose classification is unknown. USDA-APHIS has considered an apple developed using Agrobacterium as a vector agent to be a regulated article. However, a grape developed using biolistics (also known as a "gene gun" transformation, wherein plants are transformed by being bombarded with DNA coated particles that are then integrated into the plant's own genome) was not considered to be a regulated article.	Regulated in Canada if they express a novel trait.
	EU	**USA**	**Canada**
Synthetic Genomics Synthetic ~~Genomics~~ genomics does not refer to specific technologies or types of products, but rather enabling techniques that, at the most basic~~rudimentary~~ level, involve synthesizing a ~~piece of DNA~~ nucleotide sequences to be used in generating ~~that is identical in sequence to an existing one, and inserting it into an~~ organisms ~~or~~ biological entities or organisms. Examples of products of synthetic genomics could include genetically modified organisms, living synthetic	Case-dependent regulation in the EU. If synthetic genomes are introduced into receiving environments that are not capable of continuous replication or of transferring genetic material (like those used in cell extracts ~~or protocells~~), they do not meet the definition of an organism or microorganism of the EU Directives and therefore would be outside scope of EU GMO legislation, although they may be subject to other legislation. If the entity where synthetic genomes are introduced are capable of	Not regulated in the U.S. Most plants modified by synthetic biology techniques would not be considered plant pests and therefore do not meet the definition of a regulated article as defined in USDA-APHIS regulations.	Regulated in Canada if they express a novel trait.

Comment [HS4]:

s.21(1)(a)
s.21(1)(b)

organisms, cell extracts, protocells, and sensor-effector devices. ~~organism~~	replicating or transferring genetic material, regulatory oversight would be triggered since it would fall under the definition of microorganism or organism in Point 2 of Annex I Part A of Directive 2009/41/EU.		
	EU	**USA**	**Canada**
RNA Dependent DNA-Methylation (RdDM) Genes encoding RNAs which are homologous to plant sequences, like promoter regions, are delivered to the plant cells. These genes, once transcribed, give rise to the formation of small double-stranded RNAs that induce methylation of the homologous sequences elsewhere in the genome and consequently inhibit their transcription	~~Case-dependent regulation in the EU.~~ RbDM plants with integrated foreign DNA are within the scope of GMO legislation by Annex IA Part 1 (2001/18/EC) However, RdDM plants without heritable change of their DNA sequence are excluded from GMO legislation by Annex I Part B (2001/18/EC) and Annex II Part A (2009/41/EC), when the transforming DNA is excluded from the genomes of subsequent generations;	Case-dependent regulation in the U.S. Products created through RdDM are regulated as plant pests by USDA-APHIS only when plant pests are used in the transformation process. For instance, if Agrobacterium (considered a plant pest by the USDA-APHIS) is used as a vector agent, plants made via RdDM would be considered regulated articles. If a biolistic (mutagenesis-based) transformation method is used, GE plants made via RdDM would not be considered regulated articles.	Regulated in Canada if they express a novel trait.
	EU	**USA**	**Canada**
Nuclease Technology (e.g. gene editing – Zinc Finger Nucleases; Transcription Activator-like Effector Nuclease; and Clustered Regularly Interspaced Short Palindromic Repeats) *ZFN-1*: Genes encoding ZFN are delivered to plant cells without a repair template. The ZFN binds to a specific DNA sequence and generates site-specific double strand break, and the natural DNA repair process through non-homologous end-joining leads to site-specific mutations, which consist of changes of single or few base pairs, short deletions or insertions *ZFN-2*: Genes encoding ZFN are delivered to plant cells along with a short repair template. The ZFN	Case-dependent regulation in the EU, but *regulated in most cases.* Products created through ZFN-1 and ZFN-2 are excluded from GMO legislation by Annex IB (2001/18/EC) and Annex II Part A (2009/41/EC); ZFN-3 is within the scope of GMO legislation by Annex IA Part 1 (2001/18/EC) - the DNA added by ZFN 3 is a recombinant nucleic acid and the resulting organism will be a carrier of a genetic modification because the recombinant DNA is chromosomally integrated TALENs and CRISPER would likely be within the scope of Annex IA Part 1 (2001/18/EC). If	Case-dependent regulation in the U.S., but *not regulated in most cases.* For plants derived from nuclease technology, the USDA concluded in 2011 that plants containing targeted gene deletions will not, in most cases, be regulated articles under the Plant Protection Act (unless the engineered plant is already a plant pest or if the nuclease is delivered into the plant using a plant pest vector). For applications where template DNA molecules are used, APHIS will consider case-by-case enquiries regarding the regulatory status of the plants.	Regulated in Canada if they express a novel trait.

Comment [HS5]:

Comment [ND6]:

Comment [HS7]:

Comment [HS8]:

binds to specific DNA sequence and generates a site-specific double stand break. Gene repair mechanisms generate site-specific point mutations like changes of single or few base pairs through homologous recombination and the copying of the repair template *ZFN-3*: Genes encoding ZFN are delivered to plant cells along with a large stretch of DNA, whose ends are homologous to the DNA sequences flanking the cleavage site resulting from the DNA double stand break. As a result, the DNA stretch is site-specifically inserted into the plant genome *TALENs:* Transcription activator-like nucleases are dimeric enzymes with a structure which is related to ZFNs, but the DNA-binding domain of TALENs is more flexible because it consists of modules recognizing single nucleotides in a DNA sequence. Due to their longer recognition sites, TALENs are more specific for particular genomic locations and thus cause fewer unwanted off-target effects than ZFNs *CRISPR:* CRISPR nucleases are synthetic nuclease complexes, developed from the bacterial nuclease Cas9, which is a component of the adaptive immunity system in bacteria aimed to recognize and destruct the foreign DNA. Whereas ZFN and TALEN possess protein-based DNA recognition domains, CRISPR relies on short guide RNA to locate the target DNA.	used to insert a transgene into an organism, it would likely be within the scope of GMO legislation. If used to induce point mutations or indels, then they may be outside the scope of Annex IA Part 1 (EU working groups have discussed ZFNs but not TALENs or CRISPR.)		

Nataliya Dormann - RE: CBD Notification 2015-026 - Nomination of Experts to the Workshop of the Network of Laboratorie

From: Cheryl Dollard
To: Barnola, Luis; Dormann, Nataliya; Macdonald, Philip
Date: 2015-03-09 12:53 PM
Subject: RE: CBD Notification 2015-026 - Nomination of Experts to the Workshop of the Network of Laboratorie
CC: Bergeron, Emilie

Dear Luis,
Yes, I have still been following the discussion group until a new contact has been identified. The most recent exchange was related to information gathering regarding definitions of illegal versus unintentional trans-boundry movement in different countries.
Kind regards
Cheryl

>>> Barnola, Luis 2015-03-09 11:36 AM >>>
Hi Natalyia,

I know that at some point, Cheryl was following up on some of the discussion that was taking place in this group's online forum.
Cheryl, are you still part of this expert group?

To your question, Canada's position on Art. 17, as discussed last October in preparation for MOP7, emphasized the need to focus on improving capacities to conduct science-based risk assessments, not on sampling/detection capacities (see below):

In Canada's view, further work on detection and identification of LMOs under Article 17 should be deferred until and unless a clear link is made between detection capacity and the ability to comply with obligations under this Article.

Canada is also of the view that testing and detection capacity should not be given preference over the need to improve a strong, science-based risk assessment and risk management capacity, including the assessment and management of risks associated with trials, testing, and handling of LMOs prior to approval which, in Canada's view, is the appropriate approach to dealing with the unintentional release of LMOs. Consequently, Canada supports any activity leading to further developing commonly-agreed guidance on risk assessment and risk management, carried out in a scientifically sound manner and taking into account existing internationally agreed principles and techniques.

Canada is also of the view that the Protocol is not the appropriate venue to address the trade risks associated with Low Level Presence (LLP) due to the fact that unintentional transboundary movement of LLP is not likely to have any significant adverse effects on biological diversity and therefore should not trigger emergency measures

under this article.

LB

-----Original Message-----
From: Dormann, Nataliya
Sent: March-09-15 11:04 AM
To: Barnola, Luis; Macdonald, Philip
Subject: Fwd: CBD Notification 2015-026 - Nomination of Experts to the Workshop of the Network of Laboratorie

Not sure what would be the current GoC position...

>>> secretariat <SECRETARIAT@cbd.int> 2015-03-09 10:54 AM >>>
Date: 06 March 2015

From: Executive Secretary, Convention on Biological Diversity

To: Cartagena Protocol on Biosafety National Focal Points, CBD National Focal Points (where CPB focal points have not yet been designated), BCH National Focal Points and Relevant Organizations

Subject: Nomination of Experts to the Workshop of the Network of Laboratories for the Detection and Identification of Living Modified Organisms, Ispra, Italy, 9-11 June 2015

Thematic area: Cartagena Protocol on Biosafety

Action: Action required by 15 April 2015

Ref.: SCBD/BS/CG/MPM/DA/84400

NOTIFICATION

No. 2015-026

Madam/Sir,

In its decision BS-VII/10, the Conference of the Parties serving as the meeting of the Parties to the Cartagena Protocol on Biosafety (COP-MOP) requested the Online Network of Laboratories for the Detection and Identification of Living Modified Organisms to continue working with a view to achieving the operational objectives of the Strategic Plan for implementation of the Protocol (The Strategic Plan for the Cartagena Protocol on Biosafety for the period 2011-2020 is available at http://bch.cbd.int/protocol/issues/cpb_stplan_txt.shtml) that are relevant to the detection and identification of living modified organisms (LMOs) and implementation of Article 17 on Unintentional Transboundary Movements.

Furthermore, the COP-MOP also requested the Executive Secretary to organize, in cooperation with relevant organizations and subject to the availability of funds, capacity-building activities such as online and face-to-face training workshops on sampling, detection and identification of LMOs to assist Parties in fulfilling the requirements under Article 17 and towards achieving the relevant outcomes of the Strategic Plan.

In response to these requests, the Secretariat is currently organizing a series of online discussions under the Network of Laboratories on topics that are relevant to detection and identification, particularly in the context of unintentional and illegal transboundary movements of LMOs (available at http://bch.cbd.int/onlineconferences/portal_detection/discussions.shtml).

As a follow-up to the online discussions and with support from the Government of Japan through the Japan Biodiversity Fund, the Secretariat is organizing an international workshop with the objectives of:

(i) Designing the content for capacity-building workshops on the sampling, detection and identification of living modified organisms;

(ii) Compiling and developing, as appropriate, didactic material for the capacity-building activities referred to in (i) above; and

(iii) Continuing the development of technical tools and guidance as outlined in the operational objectives 1.6 and 1.8 of the Strategic Plan.

Accordingly, I am pleased to invite Parties, other Governments and relevant organizations to nominate representatives from their national LMO detection laboratories to take part in the upcoming workshop, which is scheduled to take place from 9 to 11 June 2015 at the European Commission Joint Research Centre (JRC) in Ispra, Italy. Each nomination is to be accompanied with the attached nomination form indicating the activities in which the nominee has been involved that are relevant to LMO detection and identification and the anticipated benefits of the workshop.

Due to the limited availability of funds for the workshop, participants from developing country Parties and Parties with economy in transition that are eligible for sponsorship will be selected from among the nominated experts on the basis of their relevant expertise, taking into account their participation in the online discussions of the Network of Laboratories, as well as geographical representation and gender balance.

Nominations are to be sent to the Executive Secretary via e-mail at secretariat@cbd.int or by fax at +1-514-288-6588. In order to enable us to finalize arrangements for the workshop in a timely manner, it would be appreciated if your nominations reach the Secretariat as soon as possible but no later than 15 April 2015.

s.19(1)

Thank you for your continued cooperation and support towards the work of the Cartagena Protocol on Biosafety.

The text of this notification is also available on the CBD website at:
http://www.cbd.int/doc/notifications/2015/ntf-2015-026-bs-ispra-en.doc.

Please accept, Madam/Sir, the assurances of my highest consideration.

Secretariat of the Convention on Biological Diversity

United Nations Environment Programme

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Montreal, Quebec, Canada

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Edward Harrison - NGS Workshop Steering Committee Meeting Notes and Revised Agenda

From: Nicole van der Lee
To: Harrison, Edward; Jennifer Holtzman; Macdonald, Philip; Schnell, Jaim...
Date: 2015-03-10 12:09 PM
Subject: NGS Workshop Steering Committee Meeting Notes and Revised Agenda
CC: Morin, France
Attachments: CFIA_ACIA_-_#6372493_-_vR_-_Next_Generation_Sequencing_Workshop_Draft_Agenda_March_2015.DOCX.DRF; CFIA_ACIA - #6372493 - v1 - Next Generation Sequencing Workshop Draft Agenda March 2015.DOCX

Hi Everyone,

As promised attached you will find a revised Agenda.

Summary of todays call:

1. Logistics

- Venue, A/V etc logistical considerations are progressing smoothly
- Phil suggested that we look into getting a block of room. Nicole to work with France to achieve this, if possible.
- Jennifer, Kevin and Edward agreed to assist Nicole and France with day of tasks such as registration (Jennifer), Table set up (Kevin), WebEx (Edward).
- Invitations for participants have been sent out. Still struggling with academic stakeholders. Phil and Kevin are tasked to look into this further.
- Invitee's will be provided with a package that contains the agenda and venue/accommodation information in the next week or so (and as they register beyond that). About 15 participants are registered to date (this includes some speakers and Steering Committee members)
- It was agreed that as invitee registrations and declines come in, adjustments will be made to the proportion of spots allocated for each stakeholder group to maximize participation by those interested.
- Most speakers are confirmed: Phil Macdonald, Two speakers, and have confirmed they wish to present but are awaiting their financial approvals. It was agreed that ' presentation is of special interest, and thus we will look into using WebEx as an alternative if he is unable to attend in person.
- A speaker meeting is being set up for March 17th or 18th with the speakers and facilitator to discuss presentation topics and provide speakers with instructions

2. Agenda

- See attached
- Updated with brainstormed panel questions and grammatical changes.
- **All SC members are encouraged to provide comments back on the questions in the Agenda by Thursday (March 12)**

3. WebEx

- Pitfalls to avoid: Audio difficulty (e.g. music playing on "on-hold" lines) was discussed as a common issue. Nicole, Edward and France to look into ways to maximize good audio potential.
- Discussion of 2 potential strategies to manage WebEx participants depending on group size. 1) 10 participants or less. Include these participants in table discussions by turning them into a "table" and encouraging discussion of their assigned question(s) via the WebEx chat function. Edward will relay a summary during plenary. 2) More than 10 participants. Participants will not be included in table discussions. They will be provided with table discussion questions that they will be encouraged to complete and email back. Nicole and Phil will also look into an online forum option through Intersol.
- For question periods Edward will relay WebEx questions that we will request be provided using the WebEx Chat function.

Thanks,
Nicole

Nicole van der Lee, M.Biotech.

Risk Assessor - Biotechnology , Plant and Biotechnology Risk Assessment Unit
Canadian Food Inspection Agency / Government of Canada
nicole.vanderlee@inspection.gc.ca / Tel: 613-773-6552

Évaluatrice des risques – biotechnologie, Unité d'évaluation des risques des végétaux et des produits de la biotechnologie
Agence canadienne d'inspection des aliments / Gouvernement du Canada
nicole.vanderlee@inspection.gc.ca / Tél: 613-773-6552

Canadian Food Inspection Agency | Agence canadienne d'inspection des aliments

(La version française suit le texte anglais)

Applications of Next Generation Sequencing and Bioinformatics for the Regulation of Novel Foods, Novel Feeds and Plants with Novel Traits Workshop

The overall objective of the symposium is to characterize the benefits and challenges with respect to the application of next generation sequencing (NGS) and bioinformatics in the regulation of novel foods, novel feeds and plants with novel traits. More specifically, we hope to:

1. Explore the benefits, limits and challenges of NGS and bioinformatics applications in relation to regulation of novel foods, novel feeds and plants with novel traits;

2. Develop an experimental plan or framework aimed to validate the technology in the molecular characterization and regulation of novel foods, novel feeds and plants with novel traits;

3. Discuss potential tools (e.g. checklist) to assist regulators in the assessment of molecular characterization data derived from this technology; and

4. Identify other emerging technology or applications that could be applied to the risk assessment of novel foods, novel feeds and plants with novel traits.

Agenda

March 30th:

8:00-8:30	**Registration**
8:30-9:00	**Opening Remarks**
9:00-10:10	**Regulators Perspectives** Canada- Philip Macdonald: 9:00-9:30 USA- 9:30-9:50 Mexico- 9:50-10:10
10:10-10:30	**Health Break/ Networking Break**
10:30-11:20	**Industry Perspectives** 10:30-10:55 10:55-11:20
11:20-12:00	**Table Discussion: Regulator and Industry Perspectives** • How can communication between regulators and stakeholders about the application of new genomics technologies to data generation and submission be enhanced to ensure that regulators are informed beforehand? • Are there additional hurdles to the use of new technologies for regulatory data generation?
12:00-13:00	**Lunch**

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13:00-15:00	**NGS and Bioinformatics focused presentations** : 13:00-13:30 13:30-14:00 14:00-14:30 : 14:30-15:00
15:00-15:15	**Health Break/ Networking Break**
15:15-16:15	**Table Discussion: NGS and Bioinformatics** • What are the benefits and limitations of the technology? • Identify any other new technologies you are aware of that may have applications in risk assessment/molecular characterization.
16:15-16:30	**Day 1 wrap up**

March 31st:

8:30-8:45	**Day 1 Re-cap**
8:45-9:30	**Panel Discussion** Panelists: Philip Macdonald,
9:30-10:15	**Table Discussion: NGS and Bioinformatics** • If you were to peer review a study that used next generation sequencing and bioinformatics to characterize a genetically engineered plant (e.g. characterization of copy number, insertion site, new ORFs, duplications/deletions/truncations): - What components of the experimental design would you review? - For each component, what would be acceptable/unacceptable? As a thought starter, you may wish to consider: depth of sequencing, use of a reference genome, quality of reference genome, algorithm, algorithm parameters, positive and negative control, read quality, unmapped reads, validation, etc. • Using stars mark your top 3 components to consider for risk assessment.
10:15-10:30	**Health Break/ Networking Break**

10:30-11:45	**Table Discussion: Experimental Plan** • Using the basic experimental template below as a thought starter, describe and/or elaborate upon components of a potential experimental plan to validate this technology. **Evaluate existing approaches and develop general NGS-based strategies and methods for the detection and characterization of known plants with novel traits and compare the outcomes to traditional molecular characterization tools.** *Tasks:* #1: Test and verify published molecular characterization methods. Identify potential problems with each method #2: Perform *in silico* experiments to test the effect of reducing sequence coverage on the accuracy of the molecular characterization for each of the crop species **Validate NGS technology and bioinformatics tools in characterizing plants with novel traits using an *Arabidopsis* model.** *Tasks:* #1: Vary sequencing parameters, such as library preparation method, sequence coverage, read length, and analysis method, using transgenic *Arabidopsis thaliana* as a model system #2: Use data to establish minimum draft standards in these areas for effective molecular characterization **The methodology will be extended for validation in crop models.** *Tasks:* #1: Using results generated previously, perform additional sequencing and *in silico* experiments with transgenic and isogenic crop species to test the draft standards and validate #2: Establish quality standards for molecular characterization using NGS
11:45-12:00	**Next Steps and Adjourn**

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Atelier sur l'application du séquençage de nouvelle génération et de la bioinformatique pour réglementer les aliments nouveaux, les aliments du bétail nouveaux et les végétaux à caractères nouveaux

L'objectif global du symposium est de définir les avantages et les défis liés à l'application du séquençage de nouvelle génération (SNG) et de la bioinformatique pour réglementer les aliments nouveaux, les aliments du bétail nouveaux et les végétaux à caractères nouveaux. Plus précisément, nous espérons :

1. Examiner les avantages, les limites et les défis de l'application du SNG et de la bioinformatique dans la réglementation des aliments nouveaux, des aliments du bétail nouveaux et des végétaux à caractères nouveaux;

2. Élaborer un plan ou un cadre expérimental pour valider la technologie de caractérisation moléculaire et la réglementation des aliments nouveaux, des aliments du bétail nouveaux et des végétaux à caractères nouveaux;

3. Discuter des outils (p. ex. liste de vérification) qui pourraient aider les responsable de la réglementation à évaluer les données de caractérisation moléculaire provenant de cette technologie;

4. Trouver d'autres technologies ou applications émergentes qui pourraient être utilisées dans l'évaluation des risques d'aliments nouveaux, d'aliments du bétail nouveaux et de végétaux à caractères nouveaux.

Ordre du jour
30 mars

8 h à 8 h 30	**Enregistrement**
8 h 30 à 9 h	**Remarques préliminaires**
9 h à 10 h	**Point de vue des responsables de la réglementation** Canada- Philip Macdonald: 9:00-9:30 USA- : 9:30-9:50 Mexico- 9:50-10:10
10 h 10 à 10 h 30	**Pause santé/réseautage**
10 h 30 à 11 h 20	**Point de vue de l'industrie** 10:30-10:55 10:55-11:20
11 h 20 à 12 h	**Discussions en petits groupes : Points de vue des responsables de la réglementation et de l'industrie** • Comment peut-on améliorer la communication entre les responsables de la réglementation et les intervenants sur l'application des nouvelles technologies de génomique dans la production et la présentation de données pour s'assurer que les responsables de la réglementation soient informés au préalable? • Y a-t-il d'autres obstacles à l'utilisation des nouvelles technologies pour la production de données relatives à la réglementation?

12 h à 13 h	**Repas**
13 h à 15 h	**Présentations sur le SNG et la bioinformatique** : 13:00-13:30 13:30-14:00 14:00-14:30 14:30-15:00
15 h à 15 h 15	**Pause santé/réseautage**
15 h 15 à 16 h 15	**Discussions en petits groupes : SNG et bioinformatique** • Quels sont les avantages et les limites de la technologie? • Connaissez-vous d'autres technologies nouvelles qui pourraient être utilisées dans l'évaluation des risques/la caractérisation moléculaire?
16 h 15 à 16 h 30	**Fin de la séance du jour 1**

31 mars

8 h 30 à 8 h 45	**Récapitulation de la première journée**
8 h 45 à 9 h 30	**Discussion entre experts** Experts : Philip Macdonald,
9 h 30 à 10 h 15	**Discussions en petits groupes : SNG et bioinformatique** • Si vous deviez examiner une étude dans laquelle les auteurs ont utilisé le séquençage de nouvelle génération et la bioinformatique pour caractériser une plante obtenue par génie génétique (ex. détermination du nombre de copies, site d'insertion, nouveaux cadres de lectures ouverts, duplications/délétions/troncations) : - Quelles composantes du plan expérimental examineriez-vous? - Pour chaque composante, expliquez ce qui serait acceptable et inacceptable. Comme point de départ à votre réflexion, pensez à la profondeur de séquençage, à l'utilisation d'un génome de référence et à sa qualité, aux algorithmes et à leurs paramètres, aux témoins positifs et négatifs, à la qualité des lectures, aux lectures non cartographiées, à la validation des méthodes, etc. • À l'aide d'étoiles, indiquez les trois composantes prioritaires à considérer dans une évaluation des risques.
10 h 15 à 10 h 30	**Pause santé/réseautage**

10 h 30 à 11 h 45	**Discussions en petits groupes : Plan expérimental** • Utilisez le modèle ci-dessous comme point de départ pour décrire et/ou préciser les composantes d'un plan expérimental visant à valider cette technologie. **Évaluer les approches existantes et développer des stratégies générales fondées sur le SNG ainsi que des méthodes de détection et de caractérisation des** végétaux à caractères nouveaux **et comparer les résultats à ceux obtenus avec des outils classiques de caractérisation moléculaire.** *Tâches* 1. Mettre à l'épreuve et vérifier les méthodes de caractérisation moléculaire publiées. Identifier les problèmes potentiels que pourrait poser chaque méthode. 2. Procéder à des expériences *in silico* pour vérifier l'effet de la réduction de la couverture de séquence sur l'exactitude de la caractérisation moléculaire de chaque espèce culturale. **Valider la technologie de SNG et les outils bioinformatiques pour la caractérisation des** végétaux à caractères nouveaux **à l'aide d'un modèle d'*Arabidopsis*.** *Tâches* 1. Avec le modèle d'*Arabidopsis thaliana* transgénique, varier les paramètres du séquençage, comme la méthode de préparation de la banque, la couverture de séquence, la longueur des lectures et la méthode d'analyse. 2. Avec les données obtenues, établir des normes préliminaires pour une caractérisation moléculaire efficace. **Cette méthodologie sera étendue à la validation dans des modèles de culture.** *Tâches* 1. Avec les résultats obtenus dans les tâches précédentes, procéder à d'autres séquençages ainsi qu'à des essais *in silico* avec des espèces culturales transgéniques et isogéniques pour vérifier les normes préliminaires et les valider. 2. Déterminer les normes de qualité pour la caractérisation moléculaire au moyen du SNG.
11 h 45 à 12 h	**Fin de l'atelier**

From: **Jaimie Schnell**
Sent: **2015-04-07 10:36:13 AM**
To:
CC: **Nicole.vanderLee@inspection.gc.ca;Sarah.Davis@inspection.gc.ca**
BCC:
Subject: **NGS workshop - Thank you!**

Dear and

PBRA would like to thank our U.S. and Mexican TTWG colleagues for your participation in our "Workshop on the Application of Next Generation Sequencing and Bioinformatics for the Regulation of Novel Foods, Novel Feeds and Plants with Novel traits" held last week. We were delighted that you were able to participate remotely and really appreciated the level of engagement and degree of feedback you provided. In the next few weeks we hope to have copies of the presentations and a report that will be shared with the workshop participants, and we would be glad to share it with both of you as well for distribution to any TTWG colleagues who may be interested.

Regards,
Jaimie

Jaimie Schnell
Risk Assessor - Biotechnology | Évaluatrice des risques - biotechnologie
Plant and Biotechnology Risk Assessment Unit | Unité d'évaluation des risques des végétaux et des produits de la biotechnologie
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Government of Canada | Gouvernement du Canada
<<File: TEXT.htm>>

From: Nicole van der Lee
To: Jaimie Schnell; NHQ-AC_Skyline_T1-1-249; Nicole van der Lee; Sarah G....
Date: 2015-04-08
Time: 2:30 PM - 3:00 PM
Subject: Syn Bio
Place: NHQ-AC_Skyline_T1-1-249

From: Jaimie Schnell [mailto:Jaimie.Schnell@inspection.gc.ca]
Sent: Wednesday, April 29, 2015 2:53 PM
To:
Cc:
Subject: RE: URGENT: Invitation to moderate a discussion in the Synthetic Biology forum

Hi

I've prepared the following as the opening text for topic 5. Please feel free to let me know if I've overlooked anything important.

Thanks,
Jaimie

****
Dear Participants of the Open-Ended Online Forum on Synthetic Biology,

Welcome to the discussion on Topic 5: "Best practices on risk assessment and monitoring regimes currently used by Parties to the Convention and other Governments ". It is a pleasure to moderate this discussion, and I would like to thank the Secretariat for inviting me to do so. The discussion on Topic 5 opens today and continues until June 8.
As you are all aware, the purpose of the Open-Ended Online Forum on Synthetic Biology is to support the work of the Ad Hoc Technical Expert Group (AHTEG) on Synthetic Biology, as indicated in decision XII/24<http://www.cbd.int/doc/decisions/cop-12/cop-12-dec-24-en.pdf> of the Conference of the Parties to the Convention on Biological Diversity. The topics selected for this round of discussion are drawn directly from the Terms of Reference for the AHTEG. As such, for this topic, the Terms of Reference state that the AHTEG will:
Building on the work on risk assessment and risk management undertaken by the Cartagena Protocol, compile information on best practices on risk assessment and monitoring regimes currently used by Parties to the Convention and other Governments, including transboundary movement, to inform those who do not have national risk assessment or monitoring regimes, or are in the process of reviewing their current risk assessment or monitoring regimes and to help those Parties and other Governments to regulate organisms, components and products from synthetic biology techniques appropriately.
As a starting point for this discussion, I'd like to summarize the work that has been completed to date on risk assessment and risk management undertaken by the Cartagena Protocol. First, I'd like to draw your attention to Articles 15 and 16 of the Cartagena Protocol<http://bch.cbd.int/protocol/text/>, which address risk assessment and risk management of Living Modified Organisms (LMOs), respectively, and Annex 3, which further addresses risk assessment of LMOs. Additional work has been done on risk assessment<http://bch.cbd.int/protocol/cpb_art15.shtml> under the Cartagena Protocol. In particular, the following three documents have been developed:

- Guidance on Risk Assessment of Living Modified Organisms<http://bch.cbd.int/protocol/guidance_risk_assessment>

- Training Manual on Risk Assessment of Living Modified Organisms in the context of the Cartagena Protocol on Biosafety<http://bch.cbd.int/cpb_art15/training.shtml>

- Summary and Comparative Analysis of Nine National Approaches to Ecological Risk Assessment of Living Modified Organisms in the Context of the Cartagena Protocol on Biosafety, Annex III<http://bch.cbd.int/protocol/cpb_technicalseries/cpb-ts-02-en.pdf>

Keeping in mind the work described above, I will now invite you to provide information on best practices on risk assessment and monitoring regimes that are currently used by Parties to the

Convention and other Governments.
Best regards,
Jaimie Schnell
****

>>> >>
2015-04-21 10:00 AM >>>
Dear Jamie,

Thank you for your prompt and positive reply to moderate the discussion on topic 5.

As you know, the Online Forum on Synbio was established by the Parties to support the work of the AHTEG. As such, the topics for discussion under the online discussion were drawn directly from the mandate of the AHTEG, as per its TOR in the annex to decision XII/24. For the discussion on topic 5, TOR states that the AHTEG will:

"(f) Building on the work on risk assessment and risk management undertaken by the Cartagena Protocol, compile information on best practices on risk assessment and monitoring regimes currently used by Parties to the Convention and other Governments, including transboundary movement, to inform those who do not have national risk assessment or monitoring regimes, or are in the process of reviewing their current risk assessment or monitoring regimes and to help those Parties and other Governments to regulate organisms, components and products from synthetic biology techniques appropriately;"

The objective of the online discussion is to provide enough material to enable the AHTEG to compile the information requested above. In your introductory message, you could recall the mandate and build upon it. You could also make reference to articles 15 (RA) and 16 (RM), and annex III of the Cartagena Protocol as well as the work done under the Protocol on risk assessment (http://bch.cbd.int/protocol/cpb_art15.shtml). We also have an issue of the biosafety technical series comparing the risk assessment approaches of 9 countries (Brazil, Canada, China, Cuba, Germany, Japan, South Africa, United States) which could be useful as a background document for the discussion (http://bch.cbd.int/protocol/cpb_technicalseries/cpb-ts-02-en.pdf).

Hope this helps. Please let me know if you have questions. Feel free to send me an initial draft of the opening message in case you need to double check something.

Thanks again for accepting to moderate the discussion.

Regards,

From: Jaimie Schnell [Jaimie.Schnell@inspection.gc.ca]
Sent: April-21-15 9:40 AM
To:
Cc:
Subject: RE: URGENT: Invitation to moderate a discussion in the Synthetic Biology forum
Dear

I'd be happy to moderate the session you propose below. How do we proceed with the opening remarks? Do I prepare a first draft or do you have further guidance for me.

Jaimie

>>>
2015-04-21 9:37 AM >>>
Dear Jamie,

Thank you very much for your positive response. However, given the urgency of the matter, we had to ask another participant of the synbio forum and she accepted the invitation. My suggestion would be to revert back to our original plan, if you agree, where you would moderate the discussion on Topic 5: "Best practices on risk assessment and monitoring regimes currently used by Parties to the Convention and other Governments", which will take place from 25 May to 8 June 2015. Would you be available to moderate that discussion? If so, we could start preparing the opening remarks right away.

Thanks and have a nice day. Hopefully it is a bit warmer there than here in Montreal.

Regards,

From: Jaimie Schnell [Jaimie.Schnell@inspection.gc.ca]
Sent: April-21-15 7:57 AM
To:
Cc:
Subject: Re: URGENT: Invitation to moderate a discussion in the Synthetic Biology forum
Hi

I'd be happy to moderate a session. The only small problem is that I am unavailable on the 27th. I could prepare opening remarks in advance for posting on the 27th, but I wouldn't be able to monitor any discussion that occurred on that first day.

Regards,
Jaimie

>>>
2015-04-17 4:28 PM >>>
Dear Jamie,

I tried calling and left a message on your voicemail.

We wanted to ask if you would be available to serve as a moderator in a discussion of the Online Forum on Synthetic Biology. The discussion will focus on "Similarities and differences between living modified organisms (as defined in the Cartagena Protocol) and organisms, components and products of synthetic biology techniques" (topic 2) and will take place from 27 April to 11 May 2015.

Given your experience in biosafety and the Cartagena Protocol, we thought it would be very helpful if you could take a lead role in guiding this topic. I apologize for the short notice but we were actually planning to invite you to moderate a discussion on risk assessment, which will only take place at the end of next month, but the moderator for this topic had to step down and we are in a haste to replace her.

The task of a moderator entails preparatory work to draft an introductory message and guiding questions; posting messages during the discussion to, for example, motivate additional posts or re-direct the discussion, as needed; and preparing a summary after the closing of the discussion.

The Secretariat provides support and works closely with the moderator during each of these tasks.

It would be greatly appreciated if you could let us know as soon as possible but no later than Monday if you are available to moderate the discussion.

I look forward to hearing back from you. Thank you.

Biosafety Division
Secretariat of the Convention on Biological Diversity
United Nations Environment Programme
413 Saint Jacques, 8th floor, Montreal, QC H2Y 1N9 Canada
Tel:
Email:

[International Day for Biological Diversity 2015]<http://www.cbd.int/idb/2015/> --

[International Day for Biological Diversity 2015]<http://www.cbd.int/idb/2015/> --

[International Day for Biological Diversity 2015] <http://www.cbd.int/idb/2015/> --
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Jaimie Schnell - Synthetic Biology

From: Jaimie Schnell
To: Christine Tibelius; Jaimie Schnell; NHQ-AC_Skyline_T1-0-217; Nicole v...
Date: 2015-05-07
Time: 10:00 AM - 11:00 AM
Subject: Synthetic Biology
Place: NHQ-AC_Skyline_T1-0-217

Hi all,

There are currently online discussions occurring under the Convention on Biological Diversity on Synthetic Biology that Phil and I are involved in. The purpose of this meeting is to touch base on what our role in these discussions should be. Also, with Nicole's upcoming departure, it is timely to discuss who the lead on the interdepartmental Synthetic Biology working group will be moving forward.

Regards,
Jaimie

From:
Sent: 2015-06-04 9:17:00 PM
To: Jaimie.Schnell@inspection.gc.ca
CC:
BCC:
Subject: RE: URGENT: Invitation to moderate a discussion in the Synthetic Biology forum

Thanks, Jaimie, that's awesome.
Cheers,

From: Jaimie Schnell [Jaimie.Schnell@inspection.gc.ca]
Sent: June-04-15 8:39 PM
To:
Cc:
Subject: RE: URGENT: Invitation to moderate a discussion in the Synthetic Biology forum

Hi

We have gotten quite a flurry of activity in the last few days. It's certainly great to see. I'll be able to post a closing message on Sunday. I'll do it just before 9 pm.

Regards,
Jaimie

>>> 2015-06-04 3:38 PM >>>
Hi Jaimie,

Thanks for your last posts. The summary of yesterday was great! I am super happy that the discussion picked up momentum with quite a few very useful contributions.

The discussion will close on Monday at 1:00am GMT or Sunday at 9:00pm in Ottawa. Would you be available to send a short message, just before 9pm thanking the participants and informing that the summary will be available in due time? If so, we will simply close the forum for new posts after we see your closing message. Otherwise, we can post the closing message and close the forum.

We are closing topic 4 anyways. Please just let us know what you prefer and we will act accordingly.

Thanks,

From: Jaimie Schnell [mailto:Jaimie.Schnell@inspection.gc.ca]
Sent: Wednesday, May 20, 2015 9:38 AM
To:
Cc:
Subject: RE: URGENT: Invitation to moderate a discussion in the Synthetic Biology forum

Hi

The changes you propose are fine. I will be able to post it on Sunday.

Regards,
Jaimie

>>>
2015-05-19 5:31 PM >>>
Hi Jaimie,

Thanks for your email. Unfortunately, there is no way to queue up the messages. The discussion will open on Sunday night (24 May) at 9:00pm. It would be great if you are available to open it yourself but, it is not a problem if you cannot because I can easily post the message on your behalf. I will be doing that for the other discussion topic anyways.

On a related matter, I would like to propose to have only 2 background documents for the discussion (please see http://bch.cbd.int/synbio/open-ended/discussion.shtml#topic5). In practice what this means is that we would provide the links to the Guidance and Manual, but would not call them "background documents". The reason for that is because the Guidance is being revised and I do not wish participants to lose focus of the main topic and start discussing how good or bad the Guidance is. I made the necessary revisions to the intro message to reflect this change (attached). Would this be ok for you?

Thanks and have a nice week.

Regards,

From: Jaimie Schnell [mailto:Jaimie.Schnell@inspection.gc.ca]
Sent: Wednesday, May 13, 2015 8:04 AM
To:
Cc:
Subject: RE: URGENT: Invitation to moderate a discussion in the Synthetic Biology forum

Hi

Thank you for your suggestions. I wasn't sure what formatting was allowed, so that was very helpful. I am happy with all of your proposed changes.

Is there a way to queue up the message so that it is posted right as the discussion opens?

Regards,
Jaimie

>>>
2015-05-12 4:47 PM >>>
Hi Jaimie,

Sorry for taking so long to get back to you. Things are a bit hectic in the office these days.

The intro message is great. I only made some adjustments to the formatting because the forum tool does not allow for embedded hyperlinks, italics, bold, etc. Also, I added one document to the list of background documents and changed the order in which the docs appear. Please check and let me know if you think it is ok.

Many thanks,

From:
Sent: 2015-06-09 4:33:12 PM
To:
Jaimie.Schnell@inspection.gc.ca

CC:
BCC:
Subject: RE: ISBGMO14 - scientific programme committee - an update

Excellent summary and progress. Some thoughts that occurred to me as I read through the document (I figure better to write them down now, then wonder what they were later...).

1 - Nice to know that the majority of the work is to be done by 3-4 members - do we get to nominate who these should be? (just kidding).

2 - I think that there is general agreement on the "general theme" - the bullet points are attempts to find a phrase or logo to express that the idea.

I like the 1,2,3 plenary session concepts. Something to add to session 2 might be the idea that while protection goals (or even data requirements) might differ across geographies due to legislation, social needs, environment differences - that some basic study concepts can be harmonized. For example, use of 20% as a limit for control mortality? Transparency in describing methods, results, analysis, etc. So build from a "can we agree on a ladybird beetle study design?" to a "can we agree on a trigger value to move between tiers" to a "can we agree on an acceptable end point" etc.

In session 3 - I think that proportionality of data requirements is a possible talk, but I would not list it as an overall theme for the session. One addition, although it could scare some folks, is to bring in someone to chat about Synthetic Biology as a "future."

2.3 Specific themes

Types of evidence needed for ERA - unintended effects. I was thinking that this discussion might not be limited only to unintended effects. I think the discussion could be generalized - for example, another topic that could be discussed is what you do when you have data gaps. I can envision scenarios where the mode of action has not been fully defined. Is knowledge about the MOA really critical to a safety decision?

Gene flow - One topic that could be discussed is "are there areas of the world where gene flow is not a problem?" For example, Japanese regulators regularly ask for detailed studies to show that imported maize won't become a weed in Japan. It seems that by now we should be at the point to put together a map showing where gene flow might be an issue to consider, and other areas where it just isn't.

Data transportability - I like the idea of asking regulators why data isn't transported more. There has been some work done in South America on data transportability. Maybe (ILSI Argentina) would be willing to put something together. I think that a panel discussion might work? Or perhaps some small breakout groups in a workshop setting?

I am not a big IRM fan in terms of biosafety discussion - but could be persuaded to be less pessimistic if it was broadened to include "if resistance occurs, then what?" Meaning, an overall risk assessment of what happens as older control techniques need to be brought back into

service to control the now resistant pests. One struggle I have with ISBGMO is that sometimes the sessions seem to look at only GM crops as if they were used by themselves and not as part of an overall agricultural system. So resistance in terms of overall agroecosystem risk assessment might be an interesting discussion.

Stacks - this topic is currently important in both Europe and Asia.

Insects - as I indicated in my previous email, in the past this session has been highly theoretical and forward looking, but by March 2017 we will have several examples of actual release of GM insects.

Synthetic Biology - I brought this topic up because I am current in the midst of a Cartegena Protocol - Ad Hoc Technical Committee discussion on the topic of SynBio and how it relates to the CP. If there is to be a discussion about ERA for SynBio organisms (and I think there will be), then I would rather see this discussion at ISBGMO rather than someone forming an entirely new group to talk about it. I suggested above that this might be an interesting presentation for the "future" plenary, however, I would rather see it presented in the middle of the meeting, possibly even as a. My reason is that some discussions of SynBio can be pretty distressing to some folks - the idea of entirely new organisms without "isolines" or entirely new gene constructs representing pieces of several different proteins - is new territory. At the same time, I believe that standard principles of risk assessment will work... problem formulation, exposure, hazard, etc.

From:
Sent: Monday, June 08, 2015 7:45 AM
To:
Jaimie Schnell;
Cc:
Subject: ISBGMO14 - scientific programme committee - an update

Dears,

A brief message to inform you that is also on board of the SPC, and that the composition of the SPC is now set.

The updated programme outline is attached for your consideration. It integrates most of the received input so far. Thanks for this!

The ISBR Board of Directors is planning a telephone conference in JUNE, and I will be happy to brief them about the progress made so far.

If you have additional suggestions to offer in the meantime, then please shoot.

Best,

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From: **Jaimie Schnell**
Sent: **2015-07-13 2:49:11 PM**
To: **synbio@cbd.int**
CC:
BCC:
Subject: **Re: REMINDER: Informal consultation: Availability to participate in AHTEG on Synthetic Biology**

Dear

Please accept my regrets that I will not be available to participate in the AHTEG on Syntethic Biology at this time. If the Secretariat is looking for a Canadian representative, I would like to provide my support for Jim Louter. He was actively engaged in the online discussions and did an excellent job of providing a comprehensive Canadian perspective.

Regards,
Jaimie

>>> Synbio <synbio@cbd.int> 2015-07-13 11:55 AM >>>

Dear Jaimie,

In decision XII/241 , the Conference of the Parties established an Ad Hoc Technical Expert Group (AHTEG) on Synthetic Biology with terms of reference contained in the annex to the decision, and requested the Executive Secretary to convene a moderated open-ended online forum to support the work of the AHTEG.

To implement the various elements of the decision in a systematic manner, the Secretariat put in place a continuous process comprising: (i) submission of information on synthetic biology; (ii) an open-ended online forum with online discussions on specific topics; (iii) one face-to-face meeting of the AHTEG; and (iv) peer-review of the outcomes of the AHTEG. The outcomes of this process will be submitted for consideration by the Subsidiary Body on Scientific, Technical and Technological Advice (SBSTTA) at its twentieth meeting, which is scheduled for April 2016.

In line with the calendar of activities (http://bch.cbd.int/synbio/calendar/), the online discussions of the open-ended online forum are now over and the Secretariat is in the process of selecting experts to take part in the upcoming face-to-face meeting of the AHTEG. Participants will be selected by the Secretariat, in consultation with the SBSTTA Bureau and in accordance with the consolidated modus operandi of the SBSTTA, from among those who were nominated by Parties, on the basis of their expertise, participation in the Open-ended Online Forum and taking into account geographic distribution and gender balance. A limited number of experts from among those nominated by other Governments, indigenous people and local communities and relevant organizations will be invited to take part in the AHTEG as observers.

The meeting is tentatively scheduled to take place in Montreal, Canada from 21 to 25 September 2015.

The Secretariat is currently taking stock of the online discussions and, as a participant of the Open-ended Online Forum, you will be automatically considered as a potential candidate for the AHTEG. As such, we would like to informally inquire about your availability and willingness to take part in the upcoming face-to-face AHTEG meeting.

We would appreciate it if you could inform us of you availability as soon as possible, but **no later than Monday 13 July**.

If you have any questions please do not hesitate to contact us at any time. Thank you for your support towards the implementation of the activities on synthetic biology.

Kind regards,

Secretariat of the Convention on Biological Diversity
United Nations Environment Programme
413 Saint Jacques, suite 800
Montreal, QC, H2Y 1N9
Canada

Tel:
Fax: +1-514-288-6588
Web: www.cbd.int

(http://www.cbd.int/idb/2015/) ??
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From:
Sent: 2015-08-06 11:59:32 AM
To:
Jaimie.Schnell@inspection.gc.ca;

CC:
BCC:
Subject: RE: Gene drive technologies - New challenge for ERA?

Perhaps a "new technologies" or "what is the horizon" session...

Gene drives – how to do an ERA?

Synthetic Biology – would this change how ERAs are done? (I think the basic framework is still valid)

New Breeding Technologies, Crispr/CAS for example - most ERAs thus far talk about adding a gene or a gene product, but if you remove a gene, how does that affect how you do an ERA?

Maybe something about non-"crop" GMO plants? Much of our discussion has been about typical agricultural crops like maize, soy, cotton. But what about new crops that provide industrial feed stocks?

Not sure if any of these deserve a full session, but they are topics on the horizon...

From:
Sent: Thursday, August 06, 2015 2:58 AM
To:
'Jaimie Schnell'
Cc: '
Subject: Gene drive technologies - New challenge for ERA?

Perhaps another interesting topic to schedule for discussion at the next ISBGMO

http://www.independent.co.uk/news/science/gene-drives-government-science-advisers-expected-to-investigate-potentially-dangerous-gm-organisms-10436053.html

http://www.sciencemag.org/content/early/2015/07/29/science.aac7932.abstract

http://www.sciencemag.org/content/348/6233/442.abstract

transfers of data to third parties.

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From:
Sent: 2015-08-06 4:29:48 PM
To:
Jaimie.Schnell@inspection.gc.ca;

CC:
BCC:
Subject: Re: Gene drive technologies - New challenge for ERA?

Hello all

I believe ³gene drives" is the kind of technology that is going to create a lot of uneasiness in many people. I believe it would certainly be wise to include this in the program and to follow its development to invite someone who would be at the forefront of the research at the proper timer.

I believe this could be grouped with other New Plant Breeding Technologies

I also believe that for synthetic biology the current ERA framework is enough but it may be worth discussing it.

De:
Fecha: Thursday, August 6, 2015 at 10:59
Para:

, 'Jaimie Schnell' <Jaimie.Schnell@inspection.gc.ca>
CC:
Asunto: RE: Gene drive technologies - New challenge for ERA?

Perhaps a ³new technologies² or ³what is the horizon² sessionŠ

Gene drives - how to do an ERA?

Synthetic Biology - would this change how ERAs are done? (I think the basic framework is still valid)

New Breeding Technologies, Crispr/CAS for example - most ERAs thus far talk about adding a gene or a gene product, but if you remove a gene, how does that affect how you do an ERA?

Maybe something about non-³crop² GMO plants? Much of our discussion has been about typical agricultural crops like maize, soy, cotton. But what about new crops that provide industrial feed stocks?

Not sure if any of these deserve a full session, but they are topics on the horizonŠ

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Sent: Thursday, August 06, 2015 2:58 AM
To:

'Jaimie Schnell'

Cc:
Subject: Gene drive technologies - New challenge for ERA?

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http://www.sciencemag.org/content/early/2015/07/29/science.aac7932.abstract
http://www.sciencemag.org/content/348/6233/442.abstract

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From:
Sent: 2015-08-06 9:27:30 PM
To:
Jaimie.Schnell@inspection.gc.ca;

CC:
BCC:
Subject: RE: Gene drive technologies - New challenge for ERA?

Dear
Thank you for your message and for sharing this links.
Here I am sending you some comments from the Local Committee on the program proposal that you sent us.
Sorry for the delay we had our meeting last week.
I hope you all find this comments useful.
We are also identifying possible speakers and we will send an addition to the list you have, soon.
Kind regards

De:
Enviado el: jueves, 6 de agosto de 2015 02:58 a. m.
Para:
Jaimie Schnell'
CC:
Asunto: Gene drive technologies - New challenge for ERA?

Perhaps another interesting topic to schedule for discussion at the next ISBGMO

http://www.independent.co.uk/news/science/gene-drives-government-science-advisers-expected-to-investigate-potentially-dangerous-gm-organisms-10436053.html

http://www.sciencemag.org/content/early/2015/07/29/science.aac7932.abstract

http://www.sciencemag.org/content/348/6233/442.abstract

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<<File: Mime.822>>

From:
Sent: 2015-08-07 8:13:01 AM
To:
CC:
Jaimie.Schnell@inspection.gc.ca;

BCC:
Subject: RE: Gene drive technologies - New challenge for ERA?

Dears,

An idea could be to discuss it in two different contexts - GM insects and new plant breeding techniques.

Best,

From:
Sent: 07 August 2015 01:53
To:
Cc:
Jaimie Schnell
Subject: Re: Gene drive technologies - New challenge for ERA?

I agree with that current risk frameworks can deal with SynBio - but think that this would be a good presentation to have made in this session...

Sent from my iPhone

On Aug 6, 2015, at 3:31 PM, wrote:

Hello all

I believe "gene drives" is the kind of technology that is going to create a lot of uneasiness in many people. I believe it would certainly be wise to include this in the program and to follow its development to invite someone who would be at the forefront of the research at the proper timer.

I believe this could be grouped with other New Plant Breeding Technologies

I also believe that for synthetic biology the current ERA framework is enough but it may be worth discussing it.

De: "
Fecha: Thursday, August 6, 2015 at 10:59
Para:

'Jaimie Schnell'
<Jaimie.Schnell@inspection.gc.ca<mailto:Jaimie.Schnell@inspection.gc.ca>>
CC:

Asunto: RE: Gene drive technologies - New challenge for ERA?

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Gene drives - how to do an ERA?

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From:
Sent: Thursday, August 06, 2015 2:58 AM
To:

'Jaimie Schnell'
Cc: '
Subject: Gene drive technologies - New challenge for ERA?

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http://www.sciencemag.org/content/early/2015/07/29/science.aac7932.abstract

http://www.sciencemag.org/content/348/6233/442.abstract

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y se considera que está limpio.
MailScanner agradece a transtec Computers<http://www.transtec.co.uk/> por su apoyo.

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From:
Sent: 2015-08-07 11:18:16 AM
To:
Jaimie.Schnell@inspection.gc.ca;

CC:
BCC:
Subject: RE: Gene drive technologies - New challenge for ERA?

Hi

Thanks for this. I admit my ignorance on this subject as this was new on me. I agree with what others have said. ISBR should be looking ahead and facilitate a discussion on how to deal with these new technologies in a scientific way. So I would support including some talks during the conference.

Regarding your question on organization or formats, can I throw in a crazy idea? How about a pecha kucha session? These are 5-10 min talks run on a timed presentation that moves slides every minute. Presenters have to make their point in that time. This could be set up for students that may not yet have results, but have their research projects in place. They could tell us what they are doing in 10 minutes. They could even be associated with posters. We did some of these at Syngenta and they were fun, it is a dynamic way to learn what is going on without going into fine details.

See what you think.

Regards

From:
Sent: 06 August 2015 08:58
To:
'Jaimie Schnell'
Cc:
Subject: Gene drive technologies - New challenge for ERA?

Perhaps another interesting topic to schedule for discussion at the next ISBGMO

http://www.independent.co.uk/news/science/gene-drives-government-science-advisers-expected-to-investigate-potentially-dangerous-gm-organisms-10436053.html

http://www.sciencemag.org/content/early/2015/07/29/science.aac7932.abstract

http://www.sciencemag.org/content/348/6233/442.abstract

From:
Sent: 2015-08-07 12:02:09 PM
To:
Jaimie.Schnell@inspection.gc.ca;

CC:
BCC:
Subject: RE: Gene drive technologies - New challenge for ERA?

Neat idea!

FYI.

Pecha Kucha is a presentation format where each presenter gets 20 slides each of which is shown for 20 seconds – then automatically advances. So once you start, you have 400 seconds (6 minutes, 40 seconds) and then you are done. In some venues they apparently use the next 3 minutes to answer a question, then they move on.

It was first started by a group of architects that were tired of presentations that ran on and on. One thought that I have heard is that if you can't cover your topic in a 20x20 format, then you really aren't a very good organizer/communicator.

http://www.pechakucha.org/faq

From:
Sent: Friday, August 07, 2015 10:18 AM
To:
'Jaimie Schnell'
Cc:
Subject: RE: Gene drive technologies - New challenge for ERA?

Hi

Thanks for this. I admit my ignorance on this subject as this was new on me. I agree with what others have said. ISBR should be looking ahead and facilitate a discussion on how to deal with these new technologies in a scientific way. So I would support including some talks during the conference.
Regarding your question on organization or formats, can I throw in a crazy idea? How about a pecha kucha session? These are 5-10 min talks run on a timed presentation that moves slides every minute. Presenters have to make their point in that time. This could be set up for students that may not yet have results, but have their research projects in place. They could tell us what they are doing in 10 minutes. They could even be associated with posters. We did some of these at Syngenta and they were fun, it is a dynamic way to learn what is going on without going into fine details.
See what you think.
Regards

From:
Sent: 06 August 2015 08:58
To:
'Jaimie Schnell'
Cc:

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http://www.independent.co.uk/news/science/gene-drives-government-science-advisers-expected-to-investigate-potentially-dangerous-gm-organisms-10436053.html

http://www.sciencemag.org/content/early/2015/07/29/science.aac7932.abstract

http://www.sciencemag.org/content/348/6233/442.abstract

<<File: TEXT.htm>>
<<File: Mime.822>>

From:
Sent: 2015-08-12 3:58:02 PM
To: Jim.Louter@ec.gc.ca
CC:
Sarah.Davis@inspection.gc.ca;Jaimie.Schnell@inspection.gc.ca;Philip.Macdonald@inspection.gc.ca
BCC:
Subject: Re: SynBio - AHTEG - informal group

Jim,

Excellent – welcome!

Pity that you were not asked for the AHTEG, because your interventions were spot on.

I hope that the other Canadian who was asked is a Government official, because that would add another very much needed like-minded Party representative on the AHTEG.

If your colleague does indeed decide to decline, I very much hope that she will in the same letter recommend you are someone else of the Canadian Govt in her place, to avoid that the CBD Sec starts looking elsewhere.

Cheers

On 12 August 2015 at 18:39, Louter,Jim [NCR] <Jim.Louter@ec.gc.ca> wrote:

> Thanks I'd be happy to participate in your discussion as I am able
> to (!).
>
>
>
> Regarding your other question on the AHTEG, no, I was not asked to join
> it. Perhaps I did not participate a sufficient number of times or there
> were other factors that I didn't meet. Right now, I know of only one other
> Canadian who has been to join and she may decline.
>
>
>

> Jim
>
>
>
> *From:*
> *Sent:* August 8, 2015 3:46 AM
> *To:* Louter,Jim [NCR]; Macdonald, Philip: CFIA
> *Subject:* SynBio - AHTEG - informal group
>
>
>
>
>
>
>
> Hi Jim
>
>
>
> I very much enjoyed your interventions in the on line discussions on
> synthetic biology, and wanted to alert and invite you to an informal
> discussion group on CBD-SynBio, which PRRI facilitates (in the same way as
> we facilitate such groups on CPB related topics as ERA, SECs, and Review).
>
>
>
> FYI: This is a group of over 40 colleagues with an interest in discussing
> Synthetic Biology in international fora such as OECD, CBD etc. The main aim
> is to exchange information and views. The exchanges in this group are
> informal, and not aimed at establishing common positions. Some colleagues
> on this list actively participate in the discussions, while others are
> mainly 'listeners'. PRRI participates facilitates similar groups on various
> CPB and CBD topics, such as environmental risk assessment, socio economic
> considerations in decision making, liability and redress, review and
> assessment. All these discussions are conducted under the Chatham House
> rules.
>
>
>
> The participants are PRRI members, other researchers, members of the other
> part of the regulated community (i.e. the private sector), and regulators.
> Phil is on the list for ERA and SECs.
>
>
>
> Feel very welcome to join that list. Below I paste my latest update email
> to the group.
>
>
>
> Related question: have you been invited to join the AHTEG? Know of any
> others?
>
>
>
> Cheers

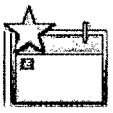
>
>
>
>
>
>
>
> Dear All,
>
> Thanks for your feedback and thoughts.
>
> Following up:
>
> AHTEG MEMBERS
>
> Thusfar I have heard learned that the following people have been confirmed
> for the AHTEG:
>
> PRRI
>
> Imperial College
>
> J. Craig Venter Institute
>
> Netherlands, GMO office
>
> Wilson Institute
>
> Brazil, Ministry of Agriculture
>
> UK, HSE,
>
> US, State Department
>
>
>
> Let us keep each other informed of any further updates.
>
> FYI: The number of AHTEG members is usually between 20 and 30. For
> example, the current AHTEG on GMO risk assessment under the Cartagena
> Protocol has 29 members (20 Party members and 9 observer members).
>
>
>
> ROLE OF AHTEGs
>
> AHTEGs are crucial in the preparatory process of the Conferences of the
> Parties to the CBD and the Meetings of the parties to the Cartagena
> Protocol (CPB).
>
> The way this typically goes is that in a meeting of the COP or MOP items
> are identified to be addressed in the next COP or MOP, such SynBio. An open
> ended on line forum is established to collect information and views, and an
> AHTEG is established to review the input provided in the online forum, to
> produce a document for consideration by the COP or MOP.
>

> Some AHTEGs meet only once, while others can continue for years.
>
>
>
> PARTICPIPATION OF OBSERVERS
>
> While the invitation from the Secretariat to participate in the AHTEG did
> not mention the term 'observer', in practice a distinction is made between
> Party members and observer members.
>
> One of the main differences is that only Party Members can vote.
>
> Other than that, it very much depends on the Chair how observers can
> participate in an AHTEG. In some AHTEGs observers have participated in the
> same way as Party members (which is how it should be, because AHTEGs are
> groups of experts), in other AHTEGs, observers could participate fully, but
> can only speak after the party members had made their contribution. This
> is a bit of an unnatural way of exchanging views among experts, but as
> Maria said, it sometimes helps to be able to speak after others have
> spoken.
>
> It is very good that Bob has asked the CBD secretariat for an explanation
> of the role of observers, and I would recommend that other new observers to
> ask for a copy of the current rules of AHTEGs.
>
> Let me underline that in my experience observers in AHTEGs have always
> participated actively and often had a very significant impact. This has
> been the case for those who want society to benefit maximally from the
> potential of modern biotechnologies, but – unfortunately – also for
> antibiotech groups. Many of us have experienced how ideo-science and
> pseudo-evidence have influenced some party members.
>
> As said, the participation of PRRI members has had quite an impact
> in MOPs, COPs and AHTEGs. Having said that, I must correct that not all
> people on this email list are PRRI members. In the past these informal
> groups did indeed only consist of PRRI members, but over the years these
> lists include other researchers, members of the other part of the regulated
> community (i.e. the private sector), and regulators.
>
> The way in which PRRI has impacted the work of AHTEGs was:
>
> - by bringing to the table the most up to date science in relation to the
> technology itself, the anticipated benefits and potential risks, where
> possible with illustrative examples,
>
> - by correcting erroneous notions about science and about the experience
> accumulated to date. Exposing crap as crap is a powerful tool.
>
> As and said, participating in an AHTEG can at times be
> frustrating, but it is important to participate. Let me also say that
> AHTEGs do not have to be a frustrating experience. Some AHTEGs in which I
> participated were actually very pleasant and an excellent way to get up to
> date with the latest developments.
>
> In addition, know that we always establish a 'back up team' on the home
> front, who can give immediate feedback through email, or search for

> articles while you sleep.
>
> Those articles can be scientific articles as well as articles from the CBD
> that are relevant to the discussions. One CBD article that is very
> important in the context of the SynBio discussions is article 16: "*Access
> to and Transfer of Technology", which in the first paragraph says:" Each
> Contracting Party, recognizing that technology includes biotechnology, and
> that both access to and transfer of technology among Contracting Parties
> are essential elements for the attainment of the objectives of this
> Convention, undertakes subject to the provisions of this Article to provide
> and/or facilitate access for and transfer to other Contracting Parties of
> technologies that are relevant to the conservation and sustainable use of
> biological diversity or make use of genetic resources and do not cause
> significant damage to the environment.*"
>
> Wishing you a good weekend
>
<<File: TEXT.htm>>
<<File: Mime.822>>

Jaimie Schnell - NGS Working Group - First draft to review

From: Jennifer Holtzman/HC-SC/GC/CA
To: <abed.zeibdawi@inspection.gc.ca>, <jaimie.schnell@inspection.gc.ca>, Jor...
Date: 2015-08-17
Time: 3:30 PM - 5:00 PM
Subject: NGS Working Group - First draft to review
Attachments: rfc2445.ics; NGS Internal Guidance for Evaluators v4.docx; c095610.ics



Invitation: NGS Working Group - First draft to review
2015-08-17 -
Chair: **Jennifer Holtzman/HC-SC/GC/CA**
Sent By: **jennifer.holtzman@hc-sc.gc.ca**

No Location Information

jennifer.holtzman@hc-sc.gc.ca Jennifer Holtzman has invited you to a meeting. You have not yet responded.

Required: abed.zeibdawi@inspection.gc.ca, jaimie.schnell@inspection.gc.ca, Jordan Bean/HC-SC/GC/CA@HWC, marina.steele@inspection.gc.ca, matthew.links@agr.gc.ca, Nicholas Petronella/HC-SC/GC/CA@HWC

Description

Hello all,

Here are the WebEx sign in details for our meeting:

Meeting Number: 550 619 280
Meeting Password:

To join the online meeting

---

1. Go to https://gts-ee-fr.webex.com/gts-ee/j.php?MTID=mf14dfcbffc7d63d880e40d1a58f0ce9d
2. If requested, enter your name and email address.
3. If a password is required, enter the meeting password:
4. Click "Join".

To join the teleconference only

Provide your phone number when you join the meeting to receive a call back. Alternatively, you can call:
Call-in toll-free number: 1-8774134788 (Canada)
Call-in number: 1-6139607513 (Canada)
Conference ID:

Hello everyone,

I've set up a Doodle poll to help with scheduling. We are looking at the third week of August. Would you please respond with your availability?

http://doodle.com/bf3f8gvdb92d336h

In the interim, Nick and Matt are discussing some of the technical issues offline. A new version of the document may be shared before our meeting, and I hope this will help us advance more quickly. It will be especially valuable to hear from the evaluators so that we can tweak the level of technical detail appropriately. For now, do please go ahead and take a look at the current draft, and/or the version with comments from Matt (sent July 26).

Thank you all in advance for your time and insights!

Best regards,

Jennifer

Good afternoon everyone,

Nick and I are happy to share with you an advanced draft of the internal guidance for evaluators. We look forward to receiving your feedback and discussing sometime in the next couple of weeks. Please let me know if you plan to be away on vacation during that time - this would be helpful for scheduling the teleconference.

Many thanks,

Jennifer

(See attached file: NGS Internal Guidance for Evaluators v4.docx)

Jennifer Holtzman, Ph.D.

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Health Canada | Santé Canada
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Government of Canada | Gouvernement du Canada

Draft internal guidance for evaluators assessing Next Generation Sequencing (NGS) data for characterization of products of biotechnology – Version 1 (July 2015)

Prepared by: ***Jennifer Holtzman, Ph.D. and Nicholas Petronella, M.Sc.***
Food Directorate, Health Canada

Table of Contents

Introduction

Companies preparing submissions to support the mandated safety assessment of new products of biotechnology are required to provide data to characterize changes that were introduced at the DNA level. Guidance for developers of Novel Foods[1], Novel Feed[2], and Plants with Novel Traits (PNTs)[3] list common elements of molecular characterization that are typically assessed. These include:

- description of all DNA added, inserted, deleted, modified
- sequence of adjacent regions, where appropriate
- number of insertion sites
- demonstration of complete or partial copies of the construct have been inserted in the genome
- organization of the inserted genetic material, e.g. copy number
- potential chimeric open reading frames created by the insertion (relevant for truncated copies)
- stability of the genetic change in a breeding program.

In the majority of submissions received from 1994 to 2015, data informing these molecular endpoints were typically produced through a combination of Southern blot experiments, PCR, and Sanger sequencing. Relatively recently, next generation sequencing (NGS) technology has been developed to the point where whole genome sequencing of eukaryotes, including crop plants with large and complex genomes, can be performed at reasonable cost, speed, and accuracy. It is expected that biotechnology companies will submit data to Health Canada and CFIA from high-throughput genomics experiments with increasing frequency in the future. The aim of this document is to provide background and guidance for evaluators completing the molecular review of these submissions who may not have direct experience with the generation and analysis of genomics data produced using NGS. This guidance will provide a framework for understanding NGS data in the context of the overall weight of evidence to support molecular characterization.

Depending on the type of genetic modification (transgenic, cisgenic, gene knockout, gene knockdown, gene editing, etc.) and the particular event, NGS data alone may not be sufficient for characterization and would typically need to be supplemented with supporting data from traditional molecular methods.

---

[1] http://www.hc-sc.gc.ca/fn-an/legislation/guide-ld/nf-an/guidelines-lignesdirectrices-eng.php#a4.1.3.1)

[2] http://www.inspection.gc.ca/animals/feeds/regulatory-guidance/rg-1/chapter-2/eng/1329298059609/1329298179464?chap=6

[3] http://inspection.gc.ca/plants/plants-with-novel-traits/applicants/directive-94-08/eng/1304475469806/1304475550733

The overall intention of this document is to enable evaluators to perform a fair assessment of NGS data in the context of the individual submission, and with equivalent robustness and sensitivity to what are possible using traditional methods, such as Southern blotting. While current genome sequencing technology offers unprecedented sensitivity, the molecular endpoints of the safety assessment will not change.

Technology overview

NGS sequencing has reached a level of maturity where it has become a routine for use in research laboratories around the world. The technology continues to experience dramatic improvements in quality with increasing read lengths and decreasing error rates. Publications where NGS was used number in the thousands, and the sequence data produced is considered to be high of fidelity.

The NGS platforms that are the main focus of this document are based on sequencing by synthesis, meaning that there is readout for each nucleotide addition by the processive action of DNA polymerase copying the template. Systems have also been developed based on sequencing by ligase (e.g., SOLiD™ fromApplied Biosystems; see https://www.youtube.com/watch?v=nlvyF8bFDwM). Here, readout is based on the highly specific hybridization of dinucleotide motifs to the template. From an operator's standpoint, there are many similarities between the platforms: sample preparation uses a kit; initial instrument setup involves preparing solutions and disposables, running wash steps, and loading the sample; the instruments handle the data collection and initial quality evaluation; and computer files containing the sequence data are outputted.

Synthesis-based experimental methods

The Sanger method for sequencing DNA was first developed in the 1970s and underwent many technical improvements to yield accurate and reliable sequence data. For single pass sequencing, it remains the gold standard. Mardis (2013) presents an overview of the principles and history of Sanger sequencing.

Second and third generation sequencing, collectively referred to as next generation sequencing (NGS), represent a different paradigm for compared to first generation Sanger sequencing. The key feature is that NGS data is produced in a massively parallel way. Millions or even billions of fragments that comprise a DNA library covering the sequence of interest (e.g., a whole genome) are sequenced simultaneously, meaning that the raw data output is very large. In practice, this is achieved by immobilizing the library fragments onto a surface or a bead and amplifying the fragments in situ. This results in dense clusters of clonal fragments that can be identified by a physical location, or address, to microscopic resolution. Subsequently, DNA polymerase is used to synthesize copies of the fragments, coupling each nucleotide incorporation step with simultaneous detection by the instrument. Exactly what is detected – fluorescence labelled nucleotides, change in pH with addition of each nucleotide, etc. – depends on the particular system. The capacity and technical specifics continue to evolve rapidly and are beyond the scope of this document; the common basic elements are summarized in the appendix. At the time of this writing, three major companies provide NGS platforms with distinct features, Illumina, Ion Torrent, and Pacific Biosciences. Each company produces a range of units with varying capacities and price points. Features of the platforms are also summarized in the appendix[4].

Another significant advantage of NGS over Sanger is that special custom designed primers are not required. Each library fragment is ligated to short adapter sequences that serve the dual purpose of attaching the library to the surface and priming synthesis. A different adapter is attached to each end of the fragment to enable sequencing in both directions. This generates what is termed paired-end reads (see below).

Raw data output

Massively parallel sequencing is highly efficient with respect to cost, time, and throughput for a run. Individual reads range in length from about 100 to 100,000 base pairs depending on the platform. The raw output of NGS sequencing is a text file containing all the read sequences in a format termed FASTQ. In FASTQ files, each nucleotide in the sequence is accompanied by a quality value that is determined by the sequencing machine at the time of data collection. An example is shown in the appendix. FASTQ files can range in size from a few hundred megabytes to 10 gigabytes. As is the case with Sanger sequencing, the read length achievable with NGS is dictated by the quality of the sequence data, which drops after a read reaches a certain length.

Depending on the quality of the raw data, additional filtering may be required to remove poor quality sequence, and this is based primarily on a quality metric termed the Phred score. The Phred score denotes a logarithmic relationship to the error probability. For example, a Phred score of 30 means that the chance that this base is called incorrectly is one in 1000, while a score of 20 means that the chance of an incorrect call is one in 100. For cases where the raw data is of very high quality, no further filtering step would be needed before further data processing. Figure 1 shows an example of how the Phred scores tend to decrease as the length of a read increases, but not drastically. Note that both the overall Phred scores and the read lengths increased significantly for experiments performed in 2015 compared to 2013. Given that each fragment is typically sequenced twice, once in the 5′ → 3′ direction, and once in the 3′ → 5′ direction, the confidence in a read sequence is very high.B.

Phred score

B.

B.

Phred score

Phred score

Accuracy of NGS data

Critics of new sequencing technology often cite the higher error rate compared to Sanger sequencing.

[4] For a quick visual overview, see the following videos:
Illumina: https://www.youtube.com/watch?v=HMyCqWhwB8E
Ion Torrent: https://www.youtube.com/watch?v=WYBzbxIfuKs
Pacific Biosciences: https://www.youtube.com/watch?v=v8p4ph2MAvI

Phred score

This observation applies to individual reads, which in practice are never considered in isolation. In reality, NGS methods are very accurate, and both experimental and data processing improvements contribute to this high fidelity.

From the laboratory side, NGS experimental protocols include steps for the user to follow which are designed to minimize error. Carry-over error (leftover sequences from a previous run) can be eliminated by improved washing techniques, and also by using different adaptors from one run to the next for easy sequence filtering. Corrections can also be made at the outset of an experiment when preparing DNA fragment library. For example, the library fragments can be purified so that all fall within a defined sequence length, and diluted if the total DNA concentration is too high. Additionally, control sequences can be mixed in with the library sample in order to balance GC content, adjust the diversity of sequences, or increase the total amount of DNA, as needed. These steps mitigate a variety of technical issues that can render some of the sequences unreadable. Even with these adjustments, some fragments will intrinsically amplify better than others, so some bias is inevitable; for example, GC-rich regions and low complexity regions tend to be underrepresented compared to other sequences.

As mentioned above, the NGS machines are able to assign quality metrics to the reads and to individual nucleotide calls. During initial processing of raw data by the instrument, "bad data" is filtered out as uninterpretable and flagged as such in the output files. Experimental level error is thus handled behind the scenes, and the accuracy of the data outputted from the instrument is very high.

It was also alluded to above that each library fragment is sequenced bidirectionally to produce paired-end reads. Any drop in sequence quality with increasing read length is offset by the sequence alignment which allows simple and rapid identification of any misincorporated nucleotides, deletions, or insertions.

Typically, a well-designed NGS run will capture each nucleotide with a high level of redundancy (see discussion below on coverage). Alignment of the reads allows identification of any errors, which can be distinguished from true biological variation, such as single nucleotide polymorphisms (SNPs). During the design phase of a sequencing experiment, the user should calculate the coverage required to achieve a desired level of accuracy. This is especially useful and effective when using platforms that produce relatively higher error rates on raw reads.

The overall error rate can be determined by sequencing a set of reference genes or a whole genome and comparing to a high quality reference gene or assembled genome. It is fair to consider that an intermediate level user can produce sequence data of very high quality using NGS.

Coverage

Coverage depth. The depth of coverage refers to the number of times a given nucleotide at one position is covered. Figures 2 and 3 show schematically a series of reads aligned to a region of a genome. The reads can be imagined as forming a tile pattern where each nucleotide in the genomic sequence is captured by a varying number of aligned reads. This number is termed the depth of coverage. The expected average global coverage for a genome (or genomic region) that is sequenced by NGS is calculated using the Lander-Waterman equation

$$C=LN/G \qquad (1)$$

where C is the coverage, G is the haploid genome length, L is the read length, and N is the number of reads. This equation is typically used during the initial study design to determine the total reads that would be needed to cover the genome. The coverage depth can also contribute to reducing overall error. For example, if the single read error rate is 1 %, eight-fold coverage can reduce this to 10^{-16} (Schatz, 2010).

Coverage uniformity. It is important to note that coverage is almost never evenly distributed throughout the entirety of the genome. Drops in coverage are frequently observed over certain regions, and some areas may not be covered at all. The reason for this observation is not well understood at this time, however the question of how different characteristics of a genome impact sequence coverage is a topic of active investigation by genome scientists and platform developers. These characteristics could include, for example, richness in AT and various other nucleotide motifs.

How much coverage is adequate to achieve credible results from a sequencing study? There is no set threshold for what coverage is acceptable, in part due to the aforementioned phenomenon of uneven coverage. The other major consideration is whether the conclusions are congruent with the data provided, and this would have to be assessed on a case by case basis. For example, relatively low coverage (e.g. 2-5X on average) may be sufficient to support a conclusion that an insert or modification is present in the event genome. A similar coverage level might not be sufficient to support a claim that a particular genetic element is absent, especially if there are significant gaps in the coverage. The evaluator would need to use his or her best judgement and consider all the molecular data and rationales presented in order to assess the validity of the petitioner's conclusions.

Coverage breadth. This refers to the length of the genome that is covered by the NGS reads. If the number of reads is too few and coverage is too uneven, gaps would appear in the sequence.

Computing needs

Concurrently with the rapid innovations in sequencing technology, informatics capacity has kept pace in order to handle the data storage and analysis challenges, since whole genome sequencing studies can produce hundreds of gigabytes worth of raw data. Bioinformatics tools have been developed to process sequence data, and many of these are open source. It is important to note that storage and computational requirements vary greatly and depend on the goals and scope of the study. As will be discussed below, junction sequence analysis is typically straightforward. The power of a home PC would be sufficient to perform a simple search of reads. More sophisticated analysis may involve assembling reads into larger contigs, which can be computationally intensive. Similarly, a study involving alignment of multiple plant genomes might require a dedicated server to complete in a reasonable time. For complex cases, the petitioner would need access to expertise in bioinformatics in order to ensure that the data is handled in a way that is valid and interpretable. Likewise, evaluators should consult with our in-house bioinformatics experts if there is any question about how data was treated and presented.

Box 1: Demystifying Computer Science Terminology

Algorithm: An algorithm is loosely defined as a process of set rules to be followed in calculations or other problem solving operations, especially by a computer. Algorithms, by their very nature are complex and often sophisticated. The best algorithms are elegant, and more often than not, the most efficient way of solving a problem. Algorithms involve mathematics and modelling. The algorithm is the very core of many programs, but it is not the entirety. In order to understand an algorithm, a good amount of computer science and mathematics knowledge is typically required. Petitioners should not be required to explain their algorithm unless they have created a novel one. Most algorithms are published and a reference to the algorithm used should suffice.

Program: A program can be defined as the set of instructions within a computer which enables it to perform the various tasks required. A program can contain numerous algorithms, or none. Many programs can share the same algorithm. For example: BWA and Bowtie are two programs used in reference guided assembly. They both use the Burrows-Wheeler Transformation algorithm. A petitioner should give a brief description of the program used or created. They should demonstrate why said program was used and why the results are useful. Programs, like algorithms, can also be published. An algorithm is often embedded inside a program.

Script: A script is a short, often uncomplicated or unstructured program. Scripts can be written very fast for the purpose of performing more menial or small tasks. They are not often elegant and mostly employ the brute force tactic. A script can be used to make a file look like another (e.g. FASTQ to FASTA) or to parse and organize files. Scripts are a bioinformatician's secret weapon. They are used to automate tasks and streamline running programs on large datasets. A petitioner should not be required to explain their scripts in detail, but can instead provide a short description. A script is often used to filter, and as long as the petitioner outlines the filtering parameters that should suffice. Scripts are often intermediaries between programs in a pipeline.

Pipeline: A pipeline is a collection of programs and scripts (and sometimes even other pipelines) that allow the data to flow in a

Box 1: Demystifying Computer Science Terminology

Algorithm: An algorithm is loosely defined as a process of set rules to be followed in calculations or other problem solving operations, especially by a computer. Algorithms, by their very nature are complex and often sophisticated. The best algorithms are elegant, and more often than not, the most efficient way of solving a problem. Algorithms involve mathematics and modelling. The algorithm is the very core of many programs, but it is not the entirety. In order to understand an algorithm, a good amount of computer science and mathematics knowledge is typically required. Petitioners should not be required to explain their algorithm unless they have created a novel one. Most algorithms are published and a reference to the algorithm used should suffice.

Program: A program can be defined as the set of instructions within a computer which enables it to perform the various tasks required. A program can contain numerous algorithms, or none. Many programs can share the same algorithm. For example: BWA and Bowtie are two programs used in reference guided assembly. They both use the Burrows-Wheeler Transformation algorithm. A petitioner should give a brief description of the program used or created. They should demonstrate why said program was used and why the results are useful. Programs, like algorithms, can also be published. An algorithm is often embedded inside a program.

Script: A script is a short, often uncomplicated or unstructured program. Scripts can be written very fast for the purpose of performing more menial or small tasks. They are not often elegant and mostly employ the brute force tactic. A script can be used to make a file look like another (e.g. FASTQ to FASTA) or to parse and organize files. Scripts are a bioinformatician's secret weapon. They are used to automate tasks and streamline running programs on large datasets. A petitioner should not be required to explain their scripts in detail, but can instead provide a short description. A script is often used to filter, and as long as the petitioner outlines the filtering parameters that should suffice. Scripts are often intermediaries between programs in a pipeline.

Pipeline: A pipeline is a collection of programs and scripts (and sometimes even other pipelines) that allow the data to flow in a controlled direction into each program until completion. A pipeline can be built to fully automate a series of programs and scripts to arrive to an answer or complete an analysis. If a pipeline is used in a submission, each step of the pipeline should be described very briefly and some sort of diagram depicting said pipeline should preferably be provided.

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Analysis and data presentation

NGS molecular data has to be analysed, organized, and presented in a way that highlights the trends or observations that support the author's conclusions so that these are plain to the evaluator. A computational pipeline is needed to take the raw reads, apply error correction scripts if necessary (e.g. filtering, deduplication for cases of unequal fragment amplification to account for library bias), retrieve and organize the reads of interest, and produce figures or tables that capture the essential information about the experiment (i.e., presence of genetic elements of interest, absence, duplication, substitution, etc.). There exist online tools and libraries of scripts to accomplish each part of the pipeline. Custom code may be written that achieves the same end. Submissions should contain a description of the pipeline, potentially using a combination of visual and narrative description.

In principle, given the raw reads and the pipeline code, it would be possible to regenerate the output figures or tables. In practice, requesting these would be analogous to requesting genomic DNA samples

and probes to recreate a Southern blot, which is not done as part of the molecular assessment of the products of biotechnology. For evaluators, information about the samples, data generation, analysis, and final output are sufficient for assessing the results of an NGS study.

BLAST. The most important component of virtually any NGS processing pipeline is BLAST, which stands for Basic Local Alignment Search Tool. BLAST is the computational workhorse for read retrieval, and knowing some background information is helpful for understanding what it can and cannot do. A web-based program implementing the BLAST algorithm is currently hosted by NCBI (http://blast.ncbi.nlm.nih.gov/Blast.cgi), where users can input their sequence of interest as the query used to search for similar sequences contained in various NCBI databases. A downloadable standalone version exists as well for users who wish to conduct searches against their own sequence databases.

NCBI defines BLAST as a tool that finds regions of local similarity between sequences. The basic principles, terminology, and parameters associated with BLAST are summarized in Box 2.The program compares input, or query, nucleotide (or protein) sequences to sequence contained in a database. It then returns the database record "hits" along with an E value, which serves to rank the hits based on similarity and length of the aligned sequences. An example output from BLAST is shown in Figure 4, and a schematic showing the essential function of the algorithm is presented in the Appendix.

In classical genetics and genomics studies, BLAST output is used to infer biological meaning, such as functional and evolutionary relationships, based on sequence similarity. For the junction sequence

Box 2: Principles, Terminology, and Parameters for BLAST

The main reason why BLAST is so widely used is because of its rapidity. High processing speed is achieved by splitting queries into various word size chunks, executing multiple smaller searches, and then organizing and concatenating the results.

A complete glossary of terms used for BLAST can be found at : http://www.ncbi.nlm.nih.gov/books/NBK62051/

A full comprehensive list of all BLAST parameters can be found at : http://www.ncbi.nlm.nih.gov/books/NBK279675/

Essential terminology

Query: The query sequence is the sequence you are looking for (think querying a database). This is typically what you are trying to retrieve.

DB or subject: The DB is the sequence database. This is where you are looking for the query. For NGS studies, the subject is composed of the reads that were generated through sequencing.

E-value (Expect value): The Expect value is used instead of the P value (probability) to report the significance of matches. For example, an E value of 1 assigned to a hit can be interpreted as meaning that in a database of the current size, one might expect to see 1 match with a similar score simply by chance. The closer the E-value is to zero, the better the match.

Score: This is a number used to assess the biological relevance of a finding. The score describes the overall quality of an alignment. Higher numbers correspond to high similarity between the query and the subject.

Length: Corresponds to the alignment length, or more specifically, the total length of matching sequence between the query and the subject hit.

pident: Percentage of identical matches in an alignment.

Word size (k-tup): Determines the size in which BLAST will split up each query and subject in the search. The default word-size varies from BLAST program.

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Limitations. BLAST is an excellent tool for performing fast sequence alignments and determining if your query sequence is actually found in the database. One limitation of NGS studies that cannot be remedied by BLAST is the inability to definitively show that a query sequence is truly absent, because of course there would be no output. For these situations, an evaluator would have to rely on context, experimental details (e.g., high versus low sequence coverage for the region of interest), other experimental data (e.g. phenotype), and rationale to judge the validity for a claim that sequence has been deleted.

A large query sequence used to BLAST search the sequence read database does not have to be broken into segments in order to detect the elements in the cassette. Indeed, having very short query sequences (5-15 base pairs) can introduce complications. In these cases, BLAST parameters may need to be modified from the defaults to adjust the detection sensitivity, mainly the *word_size* parameter. Any changes from the default parameters should be indicated in the methods description.

There exist alternatives to BLAST in which the algorithm was either adapted or modified for specialized applications. One example is STELLAR (Kehr et al. 2011), which is designed for querying short sequences. The fundamentals of this program are very similar to BLAST, however there are some extra statistical evaluation steps for improved handling of smaller sequence lengths. There also exist other local aligner programs that have the same aim as BLAST but use different algorithms, such as HMMER (http://hmmer.janelia.org/) which uses Hidden Markov models. In brief, if a program other than BLAST was used, it is worthwhile to determine if it was published and read its strengths and limitations.

It is possible to imagine events whose structures could not be determined unambiguously using BLAST. For example, there would be no way to distinguish two versus three tandem repeats with no gaps in between them using simple analysis. An expert bioinformatician may be able to use partial read assembly and sophisticated analysis techniques to differentiate between hypothetical cassette structures, however additional supporting experimental data may still be needed. It should be noted that Southern blots would be equally problematic for event characterization in such cases.

As with Southern blots, insertion of endogenous sequence presents a special problem. If insertion is in tandem, the issues described above apply. If insertion is at a different locus from the original endogenous gene, it should be possible to detect unique junctions using NGS.

Presentation of junction and copy number analysis. After the reads of interest are retrieved using BLAST or another validated method, the next step is to organize the data into figures and tables. These may contain the following information:

- Annotated maps of the T-DNA and the insert locus
- Base pair coordinates that allow calculation of the length and location of the insert elements
- Base pair coordinates to relate the insert elements identified in the event to the transformation plasmid
- Depiction of the coverage that was achieved across the junction region. This can be done using a

tool such as Integrative Genomics Viewer (https://www.broadinstitute.org/igv/)

- Alignment of reads that cover the border regions between the insert and the host genome.

As for any submitted data, unexpected results and irregularities would have to be explained. Examples of figures and their captions are presented in Figures 5 to 7.

Note that assembly of short overlapping reads into larger genomic sequences, or contigs, is usually not required for junction sequence analysis. Cases where read assembly may be useful would require one of two general approaches, reference guided or de novo assembly. The considerations for these methods are discussed in the Appendix.

Items for consideration in evaluating NGS data

The general principles described above provide the background for understanding NGS experiments and analysis in general terms. Each case must be considered on its own merits and in the context of other data and information that is provided. The following checklist is intended as a guide to help evaluators as they assess a submission and formulate critical questions for the petitioner as needed. The items that are essential to provide are indicated by (**).

- ❑ Is the overall methodology clearly and succinctly explained? Literature now has good examples that petitioners could follow.
    - How is the sample prepared to generate a fragment library? Typically, a kit is used, and purification steps are included to focus the fragment size range.
    - What sequencing platform and instrument model is used? **
    - Pipeline – can be described using text and/or figures **
        - Is BLAST or another published and validated algorithm used for read retrieval? Programs with different names that are based on BLAST may be used.
        - Are the BLAST search settings changed from default? Should settings other than default be applied?
        - If filtering or parsing was performed, what is the basis for the choice of threshold? Is it clear? Do they provide just reasoning? In your opinion, is it realistic?
        - Was the query sequence short (less than 20 base pairs)? If so, does the submission mention using a different *word_size* parameter than the default?
    - Which generation from T0 was sequenced? Same considerations as for Southern blot apply.

- ❑ Analysis of quality and completeness of the sequencing data
    - o Were the raw reads filtered prior to analysis? What Phred scores were observed for the reads?
    - o What is the coverage over the regions of interest? Is the depth of coverage sufficient for the particular claim or conclusion?**
    - o Are any gaps in coverage or over-covered regions explained?
        - Overcoverage relative to average for the genome can be an indication of multiple copies or severe bias in fragment representation
    - o Is the plasmid backbone used to query the NGS read database generated in the study?
    - o Are point mutations in raw reads explained?

- ❑ Junction sequence analysis
    - o Do figures contain qualitative and quantitative data that is complete enough to support the claims for the number and location of unique inserts?
    - o Are any reads that match the insert construct that are identified at other loci explained?
    - o Is a rationale or complementary data (PCR, Sanger sequencing, traditional Southern) provided to account for any irregularities?

<u>Other points to consider:</u>

- ❑ In some cases, it may be appropriate to either spike the library with control sequences, or simply query the reads database for these sequences (e.g. endogenous housekeeping genes of known copy number; spike comparator line genome template with proportional copies of the plasmid). This might be useful for estimation of the insert copy number. In assessing the validity, genome coverage depth, breadth, and uniformity would have to be carefully considered.
- ❑ If reference guided assembly is used, the aim of the analysis should be stated. If any reads do not map to the template, these should be explained.
- ❑ Plants often have complex multiploid genomes. With traditional Southern blot analysis, the initial transformant is typically not characterized, but rather, homozygous plants that have undergone a few rounds of breeding are chosen. It is not expected that this would be any different for plants characterized using NGS. The ploidy level should therefore not complicate interpretation data.

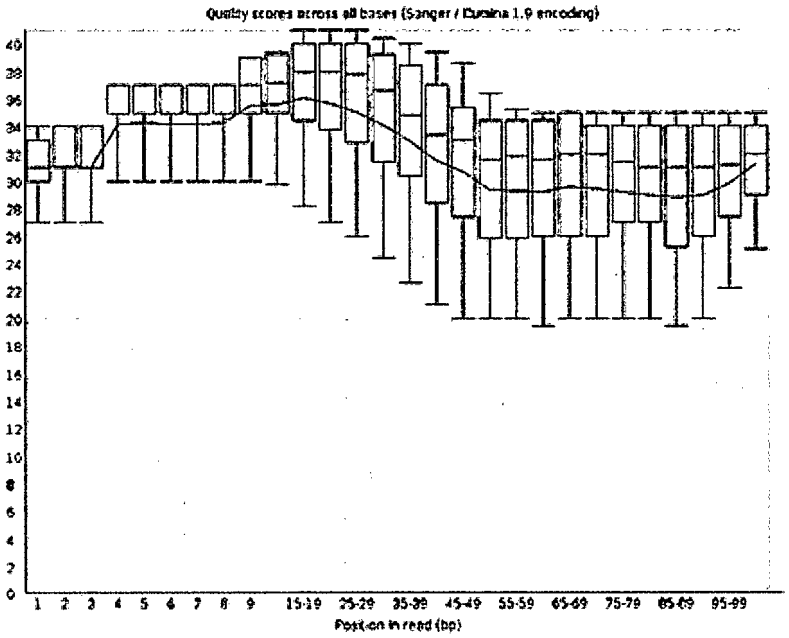
- Events produced using inserts that contain endogenous host sequence may be very difficult to characterize using NGS. The presence of unique junctions and increased copy numbers may be detected with careful experimental design. Very short insert sequences may be impossible to distinguish from true endogenous host sequence.

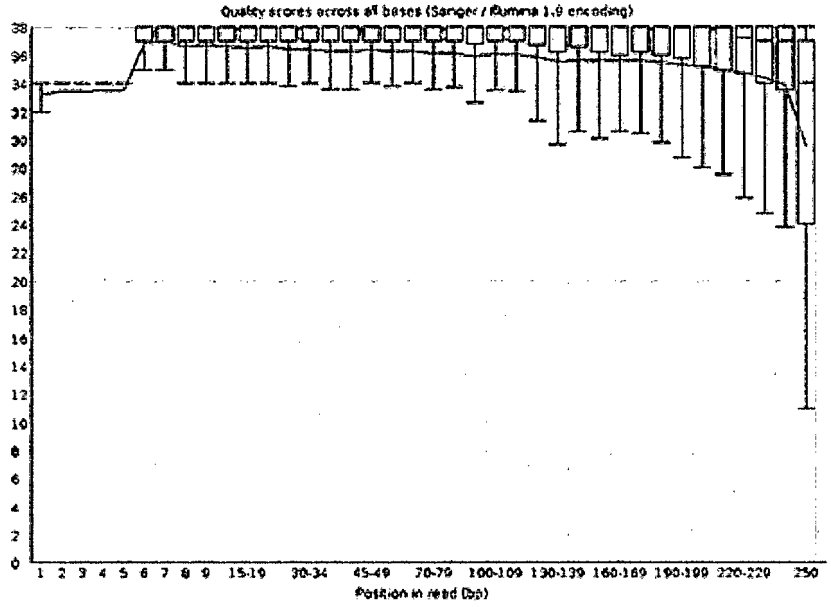
Future applications

The uses of NGS in the biomedical sciences have expanded beyond whole genome sequencing. A few examples include transcriptome profiling to assess gene expression; mapping protein•DNA and protein •RNA binding sites; metagenomics studies such as sequencing the human microbiome; and single cell sequencing to trace somatic mutations. We envision that some of these developments will have crossover applications for the characterization of genetically modified organisms in the future. The essential background provided in this document should continue to be valid in the near- to medium-term given that the instrument functions, i.e., sequence data collection and raw read processing, should be common to all platforms for massively parallel sequencing. Differences will be in the initial sample preparation and the final data presentation and interpretation. Future versions of this document will address these as needed.

Figure 1. Phred scores for a typical sequencing read output. Scores in the green zone (> 28) are of the highest quality. Those in the yellow zone (20-28) are of good quality. Scores in the red zone (<20) are of poor quality and would be filtered out using a script. Top panel, data from 2013; Bottom panel, data

from 2015.





Figures

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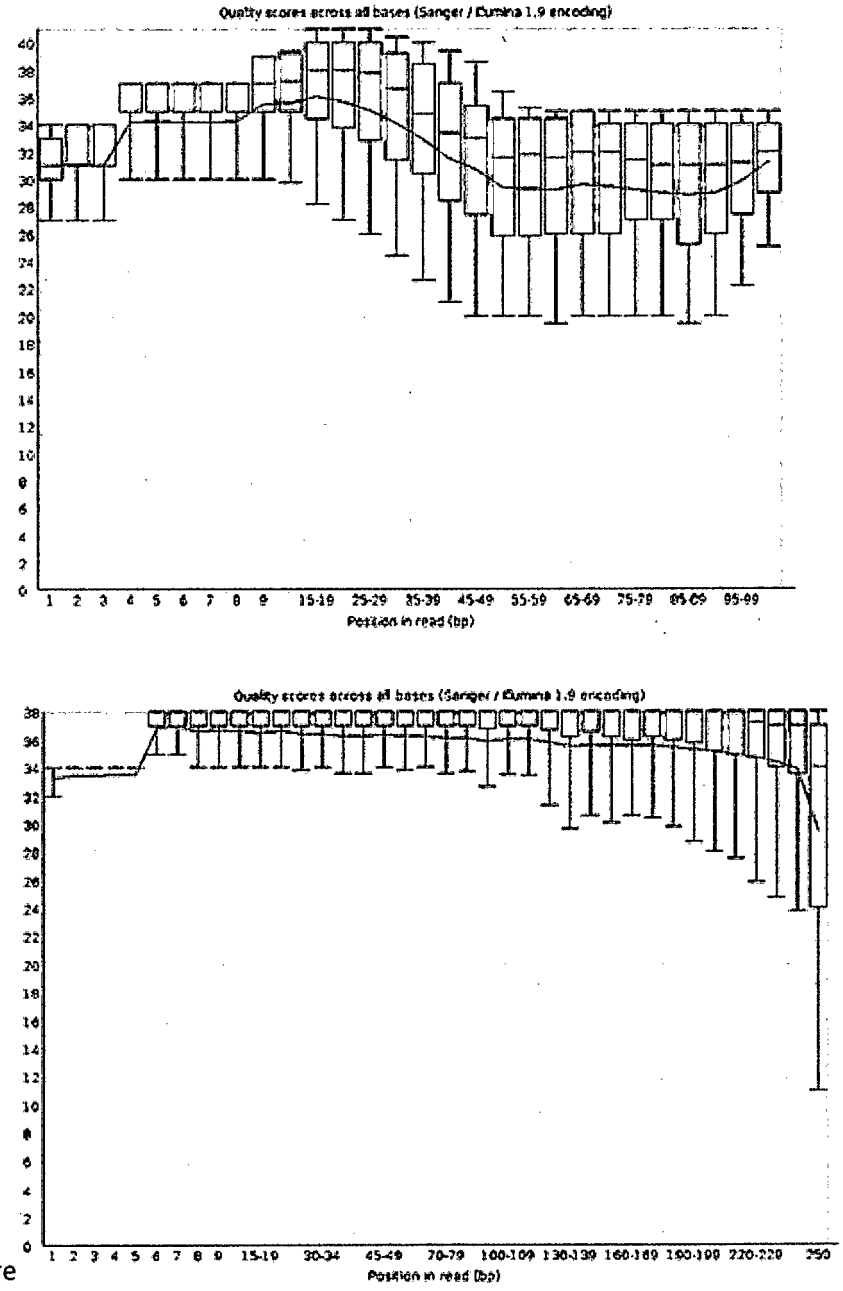


Phred score

B.

A.

Phred

Phred score

Phred
score

Figure 4. Alignment of query (input) and subject (database record) sequence from a typical BLAST run.

Sequence ID: lcl|133581 Length: 645 Number of Matches: 1

Range 1: 1 to 632 Graphics

Score	Expect	Identities	Gaps	Strand
1120 bits(606)	0.0	624/632(99%)	4/632(0%)	Plus/Plus

```
Query  43   ATTAATGTTCTATCCTCCACGCGGTTCTCATAAACCGACTTGGCTTCTTTATTTTTCCTT  102
            ||||||||||||||||||||||||||||||||||||||||||||||||| ||||||||
Sbjct  1    ATTAATGTTCTATCCTCCACGCGGTTCTCATAAACCGACTTGGCTTCTTTACTTTTCCTT  60

Query  103  TATCTTTCTCTATATATTTACACACACACGCATTTGTGCAGAGATATTCAAAGATTAGAA  162
            |||||||||||||||||||||||||||||||||||||| ||||||||||||||||||||
Sbjct  61   TATCTTTCTCTATATATTTACACACACACGCATTTGTACAGAGATATTCAAAGATTAGAA  120
```

Figure 3. Different aspects of genome sequence coverage.

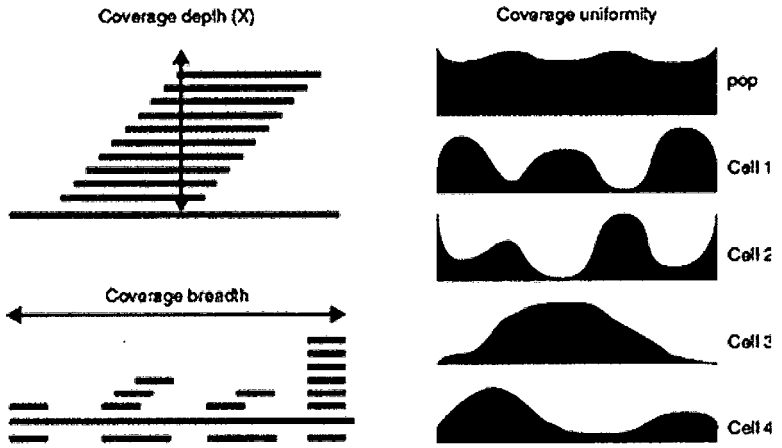
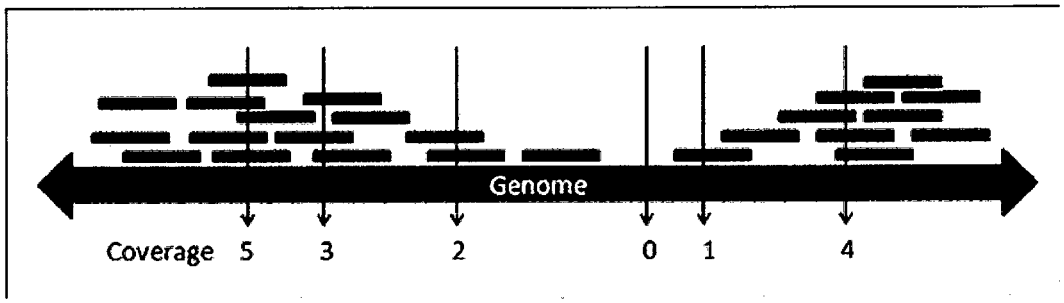


Figure 2. Illustration of depth of coverage variability for reads aligned to a region of the genome.



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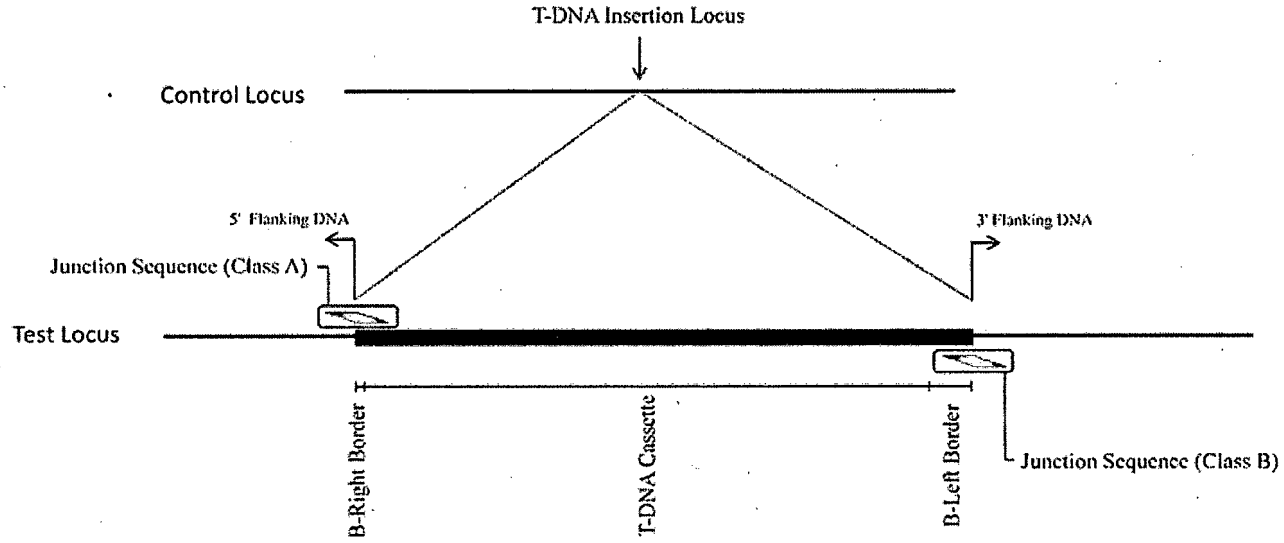
Score	Expect	Identities	Gaps	Strand

Figure 5. Qualitative representation junction sequence analysis. Figures such as this offer an easy to grasp visualization of what the petitioner is trying to explain. Even though it is not to scale, it clearly indicates that a cassette was inserted, and that the junction sequences (reads that contain both native and insert DNA) were analysed. There is no accurate depiction of coverage or how long these junction sequences are but the concept of their methods is very clear. A figure like this is drawn by hand and contains no quantitative information. (Kovalic, 2012)



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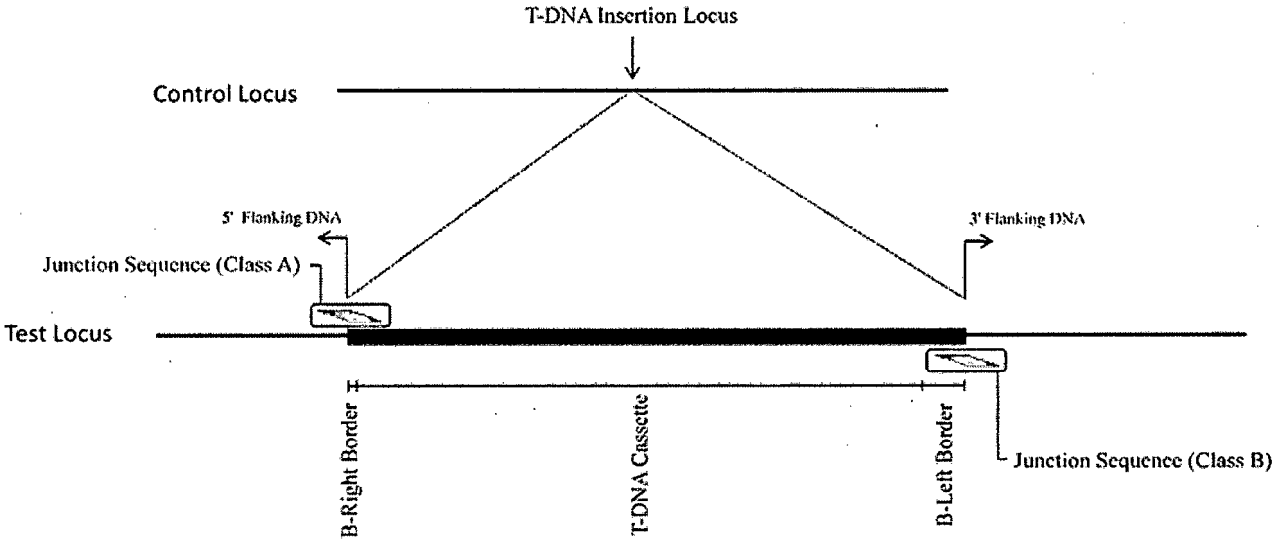
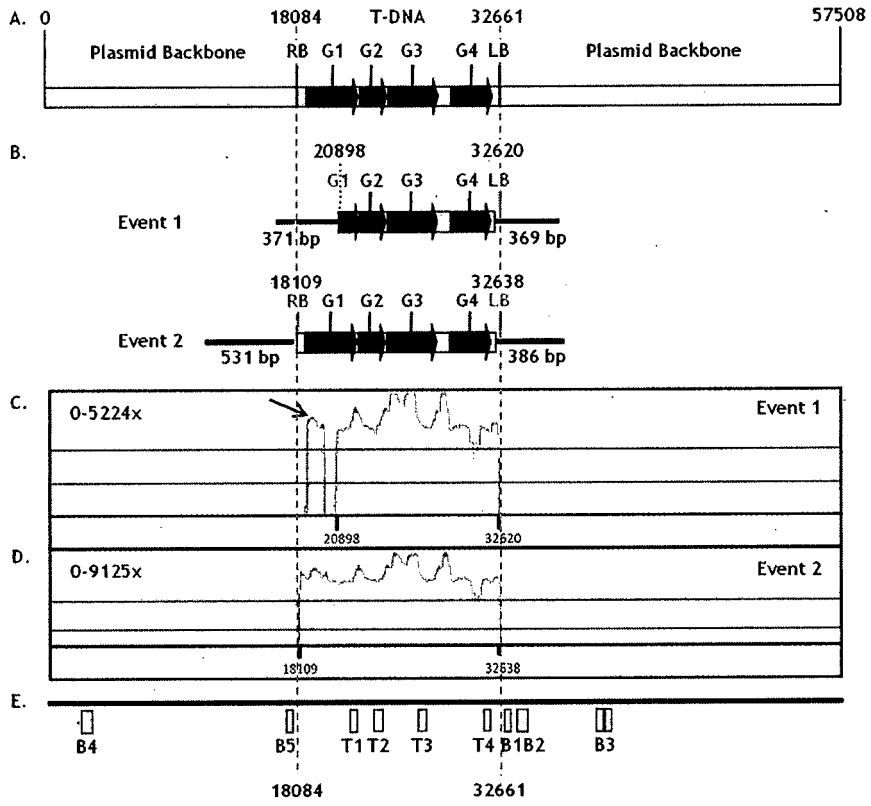


Figure 6. Complex qualitative and quantitative representation of the characterization of an insert region by NGS methods. Details such as base pair coordinates (used to give a sense of the length and location of the insert) and indicators of coverage can be clearly seen. Elements of the T-DNA are drawn to scale. (Zastrow-Hayes, 2015)



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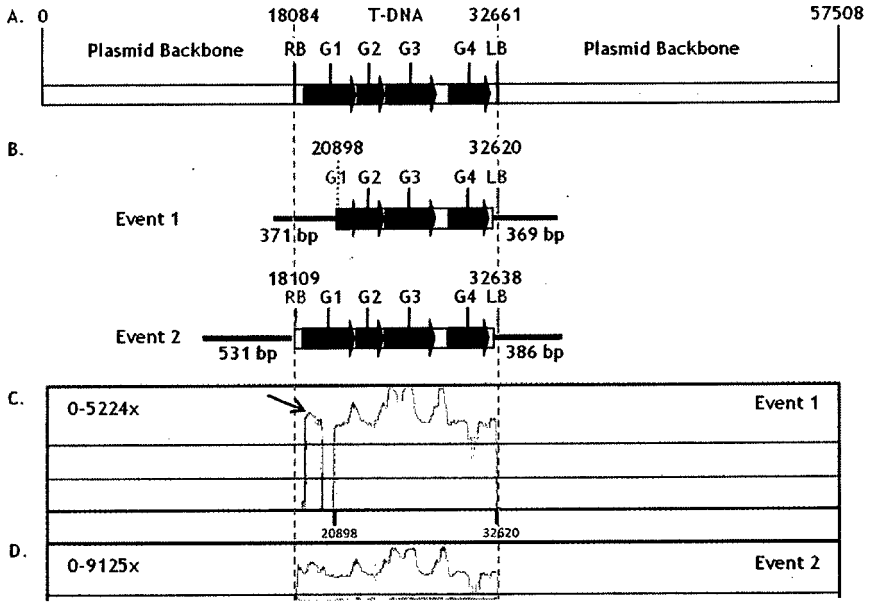

Figure 7. Alignment of reads that cover the junction sequences. (Kovalic, 2012).

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Appendix

1. Elements common to all synthesis-based NGS platforms

a. Library construction: DNA is fragmented, typically purified to retain fragments that fall within a defined range of length, enzymatically treated to blunt the ends, ligated to custom adapters. Adapters are short stretches of DNA that may serve multiple purposes, including fragment capture on a surface, templating for primer hybridization, and barcoding. The total amount of DNA in the fragment library is precisely quantitated.

b. The library is attached to a solid surface, such as a coated chip, flow cell, or bead, depending on the platform. The library fragments are captured such that there is one per bead, or for surfaces, one per point or focus. The fragments are addressable such that each can be distinguished using the machine's detection method. Once captured, the fragments may be amplified using polymerase in such a way that clonal copies become attached to the surface at high density. Amplification serves to increase the signal.

c. For platforms based on light detection (Illumina, Pacific Biosciences), the four nucleotides each have a unique fluorescence dye attached. For the pH based detection (Ion Torrent), the nucleotides are unlabelled.

d. Primers complementary to the adapter regions are hybridized to the fragments. A polymerase catalyses the incorporation of nucleotides into the strand growing from the primer. Each nucleotide addition is detected in real time and recorded by the machine.

e. Typically, each fragment is sequenced from both directions.

2. Differences between next-generation sequencing platforms.

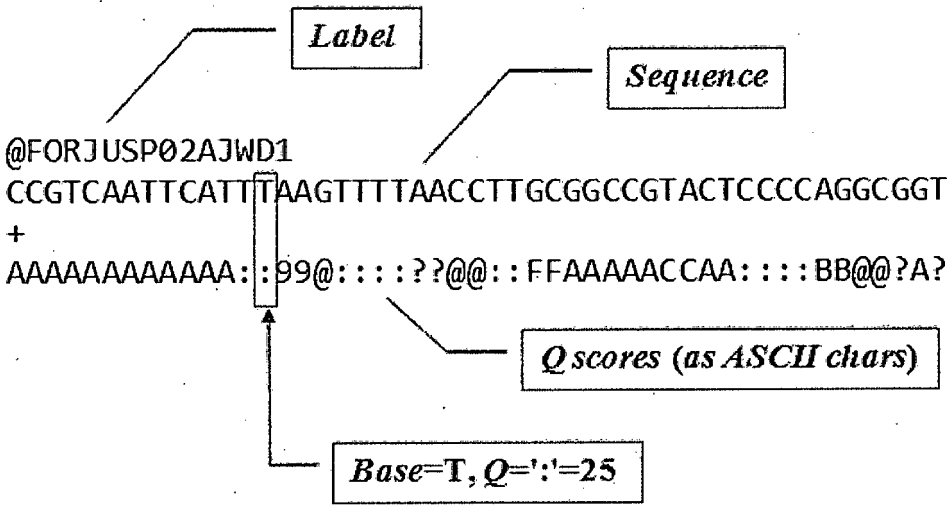
	Illumina	**Ion Torrent**	**Pacific Biosciences**	**SOLiD**
Sequencing principle	Synthesis	Synthesis	Synthesis	Ligation

Immobilization of library fragments	Oligos complementary to library adapters are covalently attached to flow cell surface	Biotin-labelled primers are used to amplify the library, which is then captured on streptavidin-coated beads. Beads are in wells.	Wells are coated in streptavidin. Biotinylated oligos capture library fragments to well surface	Beads fixed to surface
Fragment amplification	Yes (1000 copies of library template in diameter of <1 μm)	Yes	No	No
Nucleotide labels and detection	Reversible dye terminator. Different fluorophore for each nucleotide.	No labels. Release of H+ with base addition is recorded as pH change.	Fluorophore attached to terminal phosphate of the nucleotide. Removed during synthesis so native nucleotide remains. Different fluorophore for each nucleotide.	Different fluorescent dye attached to each dinucleotide, removed with successive oligo addition.
Both strands sequenced	Yes	Yes	Yes	Yes
Range of read lengths (mean)	100 - 150 bp	200 or 400 bp	250-40,000 bp (10,000-15,000 bp)	35 bp
Output per run	8 – 1800 giga bp	0.3 - 2 giga bp	50,000-80,000 reads ≅ 0.5-1.2 giga bp	
Library prep and setup time	1 day	4-5 hours	6-8 hours	
Time per run	29-252 hours	4 hours	0.5-4 hours	

3. Example of raw sequence data in FASTQ format

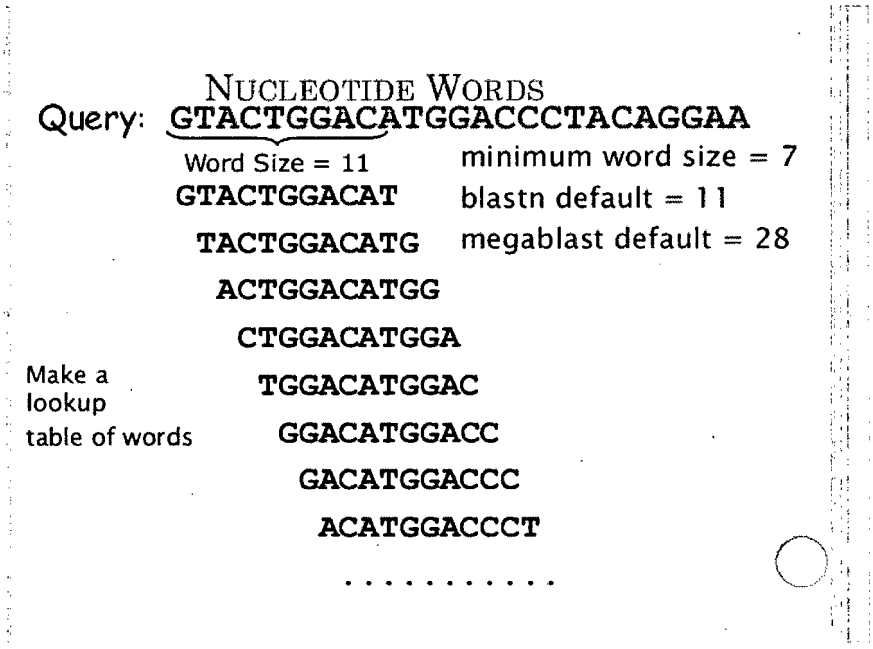
A FASTQ file is a text file that includes both the sequence data and a quality (Q or Phred) score. ASCII characters are used to represent the score for each base, which can range from 2 (low) to 41 (high). The format is not standardized, so different systems may use different score codes. Each read has four lines as shown in the sample below.

Source: http://drive5.com/usearch/manual/fastq_files.html



4. The BLAST algorithm.

This figure illustrates how a word size is used in BLAST. A word size of 11 was chosen and the manner in which the sliding window is applied can be seen.



5. Reference guided and de novo read assembly

As described in the main text, NGS sequence reads do not need to be assembled into larger contigs for junction sequence analysis. If molecular characterization would require knowledge of gene organization over a large region, for example, it is conceivable that assembly may be required. There are two ways of accomplishing this: by reference guided assembly or de novo assembly.

Reference guided assembly. In the genomics literature more broadly, reference genomes that are nearly closed (i.e., complete and containing few sequence gaps) are typically published in high profile journals. Web resources and tools for navigating the genome of a given organism may be available, and are maintained and annotated by consortia of scientists. When a genome for a related variety, event,

subspecies etc., is sequenced by NGS, the relevant reference genome may be used as a template for assembling the reads. Relying on a reference genome to guide assembly is subject to caveats. Firstly, the final assembled sequence will be biased to resemble the template. If there are natural differences in synteny (the order in which the genes are organized), these will typically be missed in the analysis. Also, any genes that are deleted in the newly sequenced genome compared to the template will be represented as gaps. Genes present in more copies relative to the template will also not be detected. A recent journal article from Health Canada researchers looked at the accuracy of reference guided assembly in the context of microbial genomes. Pightling *et al.* (2014) reported that if a reference genome is less than 99.18% identical at the nucleotide level, it is very unlikely that the assembly will be accurate. (Matt: Are there similar studies on eukaryotes?)

Three algorithms are most often used for reference guided assembly today, and these are implemented using different programs (in parentheses), some of which are available open source. These include:

- Burrows-Wheeler Transformation (BWA, Bowtie)
- Needleman-Wunch Algorithm (MOSAIK, Novoalign)
- Smith-Waterman Algorithm (SMALT)

Custom programs may exist which use these same algorithms. Also, new algorithms may be developed in the future. As long as these are published and well tested, the output should be acceptable.

De novo assembly. Reads can be assembled by sequence matching based only on alignment with one another. The practical and computational challenges of this approach can seldom be overcome for large eukaryotic genomes given that the reads are typically very short. Contig regions of a genome (or insert cassette) can, however, be assembled from filtered reads. For example, the native sequences can be filtered out of the collection of reads, and the remaining reads can be assembled. The algorithm that is most commonly used for de novo assembly today is called a De Bruijn Graph.

For those platforms that output relatively short reads, the user is faced with two challenges. First, because the shared sequence between reads is shorter, the length of contiguous sequence (contig) that can be assembled from reads is shorter. Also, repetitive regions are more difficult to assemble. With good quality sequence, it is possible to assemble very large contiguous fragments, sometime in the millions of base pairs in length.

Glossary of terms

Algorithm – A process of set rules to be followed in calculations or other problem solving operations, especially by a computer. Algorithms can be complex and sophisticated, or elegant and efficient. Often, in order to understand an algorithm, a good amount of computer science and mathematics knowledge is required.

Alignment – A way of arranging two or more sequences of DNA, RNA, or protein sequences in order to identify regions of identity, similarity, and differences. Alignments are generated by implementation of computer algorithms.

Assembly – The process of aligning and merging short sequences so as to reconstruct a larger original sequence

BLAST – Basic Local Alignment Search Tool; a tool that finds regions of local similarity between sequences

Bowtie – A freely available sequence alignment program used to assemble short DNA sequences. The assembly is typically guided by a reference genome

BWA – A program that implements the Burrows-Wheeler transform to create an index for a genome. BWA is slower than Bowtie, however it effectively aligns insertions and deletions

Contig – A contiguous series of overlapping DNA sequences, e.g. NGS reads, which reconstructs the original sequence of a chromosome

Coverage – The number of times that a given nucleotide is captured by NGS reads. The coverage depth, breadth, and uniformity serve as metrics for the quality of the sequence data

De novo assembly – An approach to assembling NGS reads through alignment with one another, without guidance from a reference genome.

FASTA – A text file format containing nucleotide or amino acid sequences, where residues are represented by their single letter codes

FASTQ – A text file format containing nucleotide sequence data from an NGS experiment. Each residue is represented by its single letter codes as well as a quality score

Jellyfish – A command line program that takes a DNA sequence in FASTA format and outputs the frequency of substrings (k-mers)

Junction – In the genome of a transgenic event, junctions are the sites of cassette insertion. Fragments DNA which capture the junctions, i.e., sequence containing both the insert cassette and the endogenous host sequence, can be detected using Southern blot or NGS-based analysis

Gap – When aligning sequences, spaces are introduced to represent sites where one sequence has more nucleotides compared to the other. It is interpreted that an insertion or a deletion ("indels) had occurred at some point when the sequences diverged.

K-mer (Word size) – A substring of DNA sequence of a given length. Both search and alignment algorithms break down raw sequence data into k-mers to produce a search tables as one step to speed up computation.

Parameters – Variables in a computer program that can be changed by the user to influence the data output.

Parse – Scripts designed to analyse or sort text, such as the output of a BLAST search.

Pipeline – A collection of programs and scripts that allow the data to flow in a controlled direction into each program until completion. A pipeline can be built to fully automate execution of a series of programs and scripts to arrive to an answer or complete an analysis.

Processive – Said of an enzyme that can catalyze sequential reactions without dissociating from its substrate. For example, DNA polymerase adds nucleotides to a growing strand processively.

Reads – DNA sequence fragments that are outputted from an NGS experiment. The size of the reads depends on the initial library preparation and the sequencing platform. The collection of sequences outputted sequences are typically of high quality and require analysis and parsing prior to interpretation.

Reference – A database of nucleotide sequence data for the genome of an organism of interest. Reference genomes are typically of very high quality and mostly assembled; gaps in assembly are often highly repetitive regions. They are also typically a hybrid of several donors and as such do not represent a single strain or individual.

Reference guided assembly – An approach to assembling NGS reads that makes use of a reference genome. This is akin to assembling a puzzle where the final picture is known.

Synteny – Conservation of the order of a set of linked genes or sequence elements at a genetic locus.

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From: **Jaimie Schnell**
Sent: **2015-08-31 1:19:39 PM**
To: **Jim.Louter@ec.gc.ca**
CC: **Sarah.Davis@inspection.gc.ca**
BCC:
Subject: **Re: FW: Invitation to AHTEG on Synthetic Biology**

Great news, Jim. I'm glad there'll be Canadian representation on the AHTEG.

Regards,
Jaimie

>>> "Louter,Jim [NCR]" <Jim.Louter@ec.gc.ca> 2015-08-31 1:15 PM >>>

FYI – got the real invitation and I have accepted.

Jim

From:
Sent: August 31, 2015 12:11 PM
To: Louter,Jim [NCR]
Cc: Synbio;
Subject: Invitation to AHTEG on Synthetic Biology
Importance: High

Dear Mr. Louter,

I am pleased to inform you that, following consultation with the SBSTTA Bureau, you have been selected from among the experts who have participated in the recent discussions under the Open-ended Online Forum to participate in the AHTEG.

In order for the Secretariat to finalize the logistical arrangements for the Group's face-to-face meeting, which is scheduled to take place in Montreal from 21 to 25 September 2015, you are kindly requested to confirm your participation in the AHTEG as soon as possible.

Kind regards,

Cartagena Protocol on Biosafety (CPB)
Secretariat of the Convention on Biological Diversity (SCBD)
United Nations Environment Programme (UNEP)
413 rue St. Jacques, Suite 800
Montreal, QC, H2Y 1N9

www.cbd.int

(http://www.cbd.int/idb/2015/)
??
<<File: TEXT.htm>>
<<File: IMAGE.png>>
<<File: Mime.822>>

From: **Jaimie Schnell**
Sent: **2015-10-07 11:34:20 AM**
To:
Sarah.Davis@inspection.gc.ca;Cecile.Girard@inspection.gc.ca;Philip.Macdonald@inspection.gc.ca;Christine.Tibelius@inspection.gc.ca
CC:
BCC:
Subject: **Further info on the outcomes of the AHTEG on Synthetic Biology**

Hi all,

I participated in a conference call with Jim Louter to listen to a verbal debrief of his participation in the AHTEG on Synthetic Biology. There were a few points that I thought were worth highlighting for you all. They're all in relation to the draft report of the AHTEG, which I've attached here.

1) Paragraph 24 includes the operational definition of Synthetic Biology. Jim pointed out that use of the term "modern biotechnology" in the definition gives it firm linkages to the Cartagena Protocol, in which modern biotechnology is defined in fairly narrow terms [*the application of: a. In vitro nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles, or b. Fusion of cells beyond the taxonomic family, that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection.*] This was preferred over biotechnology, which is defined much more broadly in the CBD [*any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use*].

2) For organisms derived from synthetic biology, there was general agreement that these will fall under the definition of LMOs and be covered by the Cartagena Protocol and overall there is a comprehensive framework in place (e.g., paragraphs 34 and 38). Jim mentioned that no one at the AHTEG could come up with a real example of an organism of synthetic biology that wouldn't be an LMO. However, there are a few places in the document where this is undermined, such as paragraphs 35 and 79.

3) Jim mentioned that there was a strong push, particularly by the NGOs, to equate non-peer reviewed publications (e.g. blog posts, website content, self-published articles) with peer-reviewed publications in terms of their value. See for example paragraph 46, which mentions that synthetic biology should be assessed with an appropriate balance between evidence as well as rational arguments. "Rational arguments" could be interpreted quite loosely by NGOs.

4) It was agreed that components and products of synthetic biology are non-living and therefore do not fall under the scope of the Cartagena Protocol (Paragraph 33). It was unclear if there were potentially gaps in oversight for products and components of synthetic biology. It was discussed that oversight likely existed, e.g. for chemicals, drugs, cosmetics, etc., but there is no single, overarching framework and so oversight is described as fragmented. Similarly, it was noted that there could be gaps in oversight under the Convention and its Protocols for components and products of synthetic biology. Jim was of the opinion that we likely had sufficient systems in place since products of synthetic biology would be equivalent to their non-synthetic biology counterparts and would be regulated similarly.

Jim expects that a new draft AHTEG report will be circulated to AHTEG members for review that should take on board final discussions. Much of the mark up in the attached document should be reflected in the next iteration. Following this, there should be additional activity at SBSTTA20 [Subsidiary Body on Scientific, Technical and Technological Advice], which is April 25-29, 2016.

Regards,
Jaimie

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<<File: AHTEG SYNBIO Draft Report_1.pdf>>

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Convention on Biological Diversity

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AD HOC TECHNICAL EXPERT GROUP ON SYNTHETIC BIOLOGY
Montreal, Canada, 21-25 September 2015

REPORT OF THE AD HOC TECHNICAL EXPERT GROUP ON SYNTHETIC BIOLOGY

INTRODUCTION

1. In paragraph 4 of decision XII/24,[1] the Conference of the Parties to the Convention on Biological Diversity decided to establish an Ad Hoc Technical Expert Group (AHTEG) on Synthetic Biology, with terms of reference contained in the annex to the decision and attached below for ease of reference.

2. In paragraphs 5 and 6 of the same decision, the Conference of the Parties invited Parties, other Governments, relevant organizations, indigenous and local communities and relevant stakeholders to submit information to the Executive Secretary relevant to the work of the AHTEG, as well as on measures undertaken in accordance with paragraph 3 of decision XII/24, including the identification of needs for guidance, and further information in response to paragraph 3(a) of decision XI/11.

3. Further, in paragraph 7 of the same decision, the Conference of the Parties requested the Executive Secretary:

(a) To make available the information submitted by Parties, other Governments, relevant organizations, indigenous and local communities and relevant stakeholders through the clearing-house mechanism of the Convention and other means;

(b) To convene a moderated open-ended online forum[2] to support the work of the AHTEG in meeting its terms of reference;

(c) To prepare an updated report on the work specified in paragraphs 3(a), 3(b) and 3(c) of decision XI/11, taking into account information submitted in paragraph 2 above and a synthesis of the outcomes of the process mentioned in (b) above and to submit these for consideration by the AHTEG;

(d) To submit for consideration by a meeting of the Subsidiary Body on Scientific, Technical and Technological Advice (SBSTTA) prior to the thirteenth meeting of the Conference of the Parties, the peer-reviewed reports of the outcomes of the process mentioned in paragraphs (b) and (c) above;

[1] Full text of the decision can be found at http://www.cbd.int/doc/decisions/cop-12/cop-12-dec-24-en.pdf.

[2] The open-ended online forum will be open to all interested participants and continue for a finite period of time.

4. In response to paragraphs 5, 6 and 7(a) of the decision, the Executive Secretary sent out a notification inviting Parties, other Governments, relevant international organizations, indigenous and local communities and other relevant stakeholders to submit information on synthetic biology. A total of 30 submissions were received, among which were eighteen from Parties, one from a non-Party and eleven from organizations. The submissions were made available through the Biosafety-Clearing House.[3]

5. Further, in response to paragraph 7(b) of the decision, the Executive Secretary invited the nomination of experts from Parties, other Governments, indigenous and local communities and relevant organizations to participate in the Open-ended Online Forum on Synthetic Biology and organized a series of moderated discussions from April to July 2015 in support of the work of the AHTEG.[4]

6. The Executive Secretary, also in response to paragraph 7(c) of the decision, prepared document UNEP/CBD/SYNBIO/AHTEG/2015/1/2 containing a report of the work done to date and analysis of the views expressed through the submissions in response to his notifications and to interventions made in Open-ended Online Forum.

7. In working towards achieving the outcomes contained in decision XII/24, the AHTEG held its face-to-face meeting in Montreal, Canada, from 21 to 25 September 2015. The list of participants to the meeting is annexed hereto as annex I.

8. Members of the AHTEG were selected in accordance with the consolidated modus operandi of SBSTTA[5] and decision XII/24, from among the nominations submitted by Parties taking into consideration geographical distribution and gender; and on the basis of their active participation in the Open-ended Online Forum and the approval of the SBSTTA Bureau. A limited number of experts nominated by other Governments and relevant organizations were also selected using the same criteria and approval process.

ITEM 1. OPENING OF THE MEETING

9. The meeting was opened at 9:30 a.m. on Monday, 21 September 2015, by Mr. Charles Gbedemah, on behalf of Mr. Braulio Dias, Executive Secretary of the Convention on Biological Diversity

10. In his opening remarks Mr. Gbedemah welcomed the members of the AHTEG, emphasized the importance of the work ahead of the Group and elaborated on the need for achieving the outcomes outlined in their terms of reference.....

11. Mr. David Cooper, Head of the Division on Scientific Assessment and Monitoring, welcomed the members of the Group, and thanked them for bringing their expertise to the meeting both face-to-face and in the online discussions that preceded the meeting. Mr. Cooper also noted that the outcomes of the meeting would be considered by SBSTTA at its twentieth meeting to be held from 25 to 29 April 2016 in Montreal, Canada.

12. Following his opening remarks, Mr. Gbedemah invited the members of the AHTEG to introduce themselves briefly.

ITEM 2. ORGANIZATIONAL MATTERS

[3] The submissions of information on synthetic biology are available online at http://bch.cbd.int/synbio/notifications/.

[4] The discussions under the Open-ended Online Forum on Synthetic Biology are available at http://bch.cbd.int/synbio/open-ended/discussion.shtml.

[5] Annex III to decision VIII/10 of the Conference of the Parties, paragraph 18.

2.1. Election of officers

13. Participants elected Mr. Martin Batič from Slovenia as Chair and Ms. Maria de Lourdes Torres from Ecuador as the Rapporteur of the Group.

14. Following his election, the Chair made an introductory statement, highlighting the importance of the task at hand and the challenges ahead.

2.2. Adoption of the agenda

15. The Chair invited the Group to consider and adopt the provisional agenda circulated by the Secretariat as document UNEP/CBD/SYNBIO/AHTEG/2015/1/1.

16. The group agreed to consider the item "Towards an operational definition of synthetic biology comprising inclusion and exclusion criteria" as the first substantive item to be discussed by the AHTEG and adopted the provisional agenda with this amendment.

2.3. Organization of work

17. The Group agreed to proceed on the basis of the organization of work contained in annex II to the annotations to the agenda prepared by the Secretariat in consultation with the AHTEG Chair and circulated as document UNEP/CBD/BS/AHTEG-RA&RM/5/1/Add.1.

18. The Group further agreed to work in plenary and to break into smaller groups, if needed.

ITEM 3. SUBSTANTIVE ISSUES

19. Ms. Manoela Miranda, of the Secretariat of the Convention on Biological Diversity, provided an overview of the outcomes of the work of the Open-ended Online Forum on Synthetic Biology and introduced the background document, UNEP/CBD/SYNBIO/AHTEG/2015/1/2, to assist the Group in its deliberations on each of the substantive items.

3.1. Towards an operational definition of synthetic biology comprising inclusion and exclusion criteria

20. In its deliberation under this agenda item, the AHTEG recognized that synthetic biology is a broad term that refers to a wide range of disciplines, techniques, potential applications and end products, and has a degree of overlap with modern biotechnology.

21. It was also noted that an operational definition needs to be understood in the context of the objectives of the Convention and the definition is aimed at assisting Parties ~~and regulators,~~ in their implementation of the provisions of the Convention.

22. In light of the above, there was support for the development of an operational definition that expresses both the notions of continuity as well as novelty in relation to modern biotechnology, and draws on elements from the text of the definition developed by three scientific committees of the European Commission[6] and included in the submission by the European Union in response to the notification issued by the Secretariat inviting submissions on information relevant to the work of the AHTEG[7].

23. Taking into account the deliberations of the AHTEG and shared views by members, the Chair proposed a draft operational definition for consideration of the Group.

24. The following is the outcome of the deliberations of the Group on an operational definition of Synthetic Biology:

> "Synthetic biology is a further development and new dimension of [modern] biotechnology that combines science, technology and engineering to facilitate and accelerate the understanding, design, redesign, [production] and/or modification of genetic materials, living organisms and biological systems."

3.2. Relationship between synthetic biology and biological diversity

25. Under this agenda item, members of the AHTEG took note of the exchange of views during the open-ended online discussions and the submissions[8] on how to address the relationship between synthetic biology and biological diversity.

26. In their deliberations, the Group highlighted several applications where organisms, components and products of synthetic biology, such as bioenergy, agriculture, pharmaceuticals and chemical production, may interact with biological diversity. These applications, the Group noted, may have both positive and negative impacts on biological diversity at different levels, including genes species and ecosystems.

27. In addressing the relationship between synthetic biology and biological diversity, the Group worked within the context of an operational definition and each of the specific three objectives of the Convention. It was noted that to facilitate discussions of the relationship between synthetic biology and biological diversity, an appropriate baseline for measuring the positive and negative impacts of synthetic biology on each of the objectives of the Convention needs to be considered and, where possible, supported by evidence-based information, including peer-reviewed data, ~~if available~~.

28. The AHTEG noted that the conservation and sustainable use of biodiversity, and the access and benefit sharing arising from the utilization of genetic resources may be affected, both positively and negatively, by living organisms resulting from synthetic biology, as well as by non-living products or components.

29. On the one hand, some members of the AHTEG further noted that there is potentially higher level of uncertainty due to the increased depth of intervention of synthetic biology in living organisms and biological systems, and emphasized, in accordance with paragraph 3 of decision XII/24, the need for Governments to take a precautionary approach when addressing threats of significant reduction or loss of biological diversity posed by organisms, components and products resulting from synthetic biology, in accordance with their domestic legislation and other relevant international obligations. On the other hand, some members of the AHTEG noted that there are mechanisms built into existing risk assessment frameworks to take into account such uncertainties in a stepwise manner as well as taking note of past experiences in existing frameworks. In this context, these AHTEG members noted that the nature of synthetic biology research and development may lead to more predictable outcomes thereby facilitating

[6] SCENIHR, SCCS, SCHER (2014) Final Opinion on Synthetic Biology I Definition. Available at http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_044.pdf

[7] Notification SCBD/BS/CG/MPM/DA/84279 available at http://www.cbd.int/doc/notifications/2015/ntf-2015-013-synthetic-biology-en.pdf

[8] Available at http://www.cbd.int/doc/notifications/2015/ntf-2015-013-synthetic-biology-en.pdf and http://bch.cbd.int/synbio/open-ended/discussion.shtml.

the risk assessment process and reducing uncertainty, and stressed that, by not adopting this technology, some countries may forfeit potential opportunities to support the three objectives of the Convention.

30. The AHTEG also noted that regulators and decision-makers may face challenges in fully addressing the potential positive and negative impacts of synthetic biology on biodiversity due to the rate at which the technologies of synthetic biology are evolving. Another aspect of the relationship between synthetic biology and biological diversity that was noted was potential positive and negative indirect effects that may need to be taken into account in the adoption and use of organisms, products and components of synthetic biology in order to ensure that the sustainable use of biodiversity is maintained.

31. Within the context of Articles 15 and 16 of the Convention and the Nagoya Protocol, the AHTEG also took note of the fact that synthetic biology may have both positive and negative impacts on the fair and equitable sharing arising from the utilisation of genetic resources. Some AHTEG members further noted that the potential for the unequitable use of digital genetic information.

3.3. Similarities and differences between living modified organisms (as defined in the Cartagena Protocol) and organisms, components and products of synthetic biology techniques

32. In considering this agenda item, the AHTEG arrived at a common understanding that the term "components" would refer to parts used in a synthetic biology process (e.g. a DNA molecule), and the term "products" would refer to the resulting output of a synthetic biology process (e.g. a chemical substance). Both terms were considered as non-living. On the basis of this understanding, the Group agreed that these non-living components and products of synthetic biology do not fall under the scope of the Cartagena Protocol on Biosafety.

33. The AHTEG deliberated on whether living organisms derived from synthetic biology fall under the scope of the Cartagena Protocol by considering both the similarities and the differences between LMOs and the living organisms developed through current and near-future applications of synthetic biology.

34. The AHTEG agreed that living organisms developed through current and near future applications of synthetic biology are similar to LMOs as defined in the Cartagena Protocol.

35. However, the AHTEG noted that it is not clear at this stage, whether or not some synthetic biology organisms, which are currently in the early stages of research and development, fall under the definition of LMOs under the Cartagena Protocol.

36. It was also noted that there are cases where there may be no consensus on whether the result of a synthetic biology application is "living" or not (e.g. protocells).

3.4. Adequacy of other existing national, regional and/or international instruments to regulate the organisms, components or products derived from synthetic biology techniques

37. Under this agenda item, the AHTEG first examined the issues on whether the components, organisms and products of synthetic biology fall under the scope of existing legislations, whether the existing legislations can adequately address the technology, and whether there are any gaps in the existing legislations.

38. Following discussions under item 3.3, the AHTEG noted that living organisms, components and products of synthetic biology fall within the scope of the Convention. However, the scope of the Cartagena Protocol and the Nagoya-Kuala Lumpur Supplementary Protocol on Liability and Redress is considered to be limited to the living organisms of synthetic biology. It was therefore noted that many components and products of synthetic biology, while covered by the Convention, are not covered by the scope of the two Protocols and possibly neither in some national biosafety frameworks.

39. The Nagoya Protocol was noted as a relevant international instrument which provides a framework for the fair and equitable sharing of the benefits arising from the utilization of genetic resources in synthetic biology. Nevertheless, the lack of clarity on how the provisions of the Nagoya Protocol apply, in practice, to synthetic biology was noted as a challenge.

40. Some members of the AHTEG noted that products of synthetic biology fall under the scope of international, regional or national instruments addressing chemicals, human pharmaceuticals, veterinary products, among others. At the national level, while some AHTEG members considered their sectorial regulations as adequate to address the products of synthetic biology, other members considered such legislations to be fragmented and/or lacking the necessary legislative regimes.

41. Some members of the AHTEG noted the following needs with regard to international regimes: (a) provisions to address the socioeconomic impacts of the components and products of synthetic biology; (b) measures to minimize the likelihood of unintentional transboundary movements of synthetic biology organisms after their release into the environment; (c) traceability tools to ensure the fair and equitable sharing of the benefits arising from the utilization of genetic resources in synthetic biology.

42. While some member of the AHTEG noted that some countries have policies and regulations to control the exchange, distribution and commercialization of the products of modern biotechnology, which could also be applied to the non-living components of synthetic biology, other members did not consider the existing national legislations to be adequate to regulate the components of synthetic biology.

3.5. Potential benefits and risks of organisms, components and products arising from synthetic biology techniques to the conservation and sustainable use of biodiversity and related human health and socioeconomic impacts relevant to the mandate of the Convention and its Protocols

43. Under this agenda item, the AHTEG considered the potential benefits and risks of organisms, components, and products of synthetic biology within the mandate of the Convention and its Protocols and taking into account the background document, submissions and interventions in the online forum.

44. In line with the operational definition of synthetic biology, the AHTEG noted that the organisms, components, and products of synthetic biology are expected to have similar positive and negative impacts on biological diversity, as those of classical genetic engineering. However, the potential positive and negative impacts of synthetic biology may be broader and more wide-ranging due to the potential of synthetic biology to engineer more complex organisms and biological systems for use in a varied range of applications.

45. Compared to classical genetic engineering, members of the AHTEG noted that a distinctive quality of synthetic biology is its rate and depth of intervention, which may lead to decreased familiarity of the organisms developed through synthetic biology in comparison with non-modified organisms. From an engineering perspective, synthetic biology aims at more predictability of the characteristics of the resulting organism. However, the level of uncertainty in risk assessment may increase with regard to the impacts to biodiversity and human health, as well as the time needed to complete the risk assessment.

46. Potential benefits as well as potential adverse effects and risks of synthetic biology applications need to be assessed on a case-by-case basis, and striking an appropriate balance between evidence as well as rational arguments.

47. Furthermore, the relationship between synthetic biology and bioethical implications on societal views towards nature, including the relationship between mankind and ecosystems, was noted as a horizontal and cross-cutting issue with respect to all three objectives of the Convention.

48. The potential benefits and risks associated with synthetic biology are dependent on the particular circumstances and context in which the application is used, for example the country in which the technology is being applied, its ecosystem and relevant production system.

49. With respect to the issue of potential benefits and potential adverse effects that may affect the implementation of the second objective of the Convention targeting the sustainable use of biodiversity, the group noted that this involves a higher level of complexity that requires the placement of synthetic biology in the context of other ongoing developments and national strategies, such as existing strategies and approaches on bio-economy, biotechnology, agriculture, biodiversity etc.

50. The assessment of the potential benefits and potential adverse effects of synthetic biology on the sustainable use of biological diversity, therefore, is challenged by the difficulty of untangling which socio-economic changes resulted from its introduction. As such, it may be necessary to introduce appropriate methods from relevant scientific disciplines to take into account socio-economic considerations.

51. Furthermore the current and foreseeable future applications of synthetic biology being considered in the assessment of potential benefits and risks are at various stages of development, ranging from the theoretical to early or active areas of research to those that are already on the market. As such the timeframe within which the potential benefits and risks associated with these applications may be realized would vary considerably.

52. The following paragraphs contain illustrative examples of potential benefits and adverse effects classified in accordance with the objectives of the Convention.

Potential benefits

53. A cross-cutting and key potential benefit of synthetic biology is the contribution to the understanding of biological systems from the molecular to the ecosystems level.

Objective 1: Conservation of Biological Diversity

54. Medical and nutritional applications may lead to healthier populations, which is a pre-requisite towards the conservation of biological diversity.

55. Using micro-organisms produced through synthetic biology to utilize biomass waste from agriculture and/or forestry more efficiently. This may reduce reliance on natural environments or land-use for agriculture and forestry.

56. Industrial applications of synthetic biology that lead to alternative production methods of products that originate from natural sources as well as chemicals or other materials.

57. Bioremediation may contribute towards restoration of ecosystems.

58. Resistance or tolerance to various stresses, such as diseases and abiotic stresses, may contribute towards species conservation.

59. Agricultural and agroforestry applications with reduced chemical pesticide/herbicide use may lead to the conservation of pollinators and other non-target organisms.

Objective 2: Sustainable use of Biological Diversity

60. Agricultural and agroforestry applications of synthetic biology such as abiotic stress tolerance or micro-organisms modified for increased nitrogen fixation may lead to restoring productivity of depleted agricultural land as well as to increased crop productivity on existing agricultural land.

61. In the area of bioenergy applications that rely on synthetic biology some models indicate the potential reduction in green house gas emissions, which will contribute to mitigating climate change and thereby contributing towards the sustainable use of biological diversity.

62. Application of gene-drive systems and other tools of synthetic biology to control agricultural pests and animal and human diseases may improve sustainable use of biodiversity and human health.

Objective 3: Fair and equitable sharing of the benefits of biological diversity

63. Provisions on the fair and equitable sharing of benefits from the use of biological diversity are addressed by Articles 15 and 16 of the Convention and the Nagoya Protocol. The availability of synthetic biology may enable the fair and equitable sharing of benefits to relevant stakeholders in developing countries through greater access to the tools of synthetic biology, therefore facilitating the transfer of knowledge and technology.

Potential adverse effects[9]

Objective 1: Conservation of biological diversity

64. Potential adverse effects and risks of synthetic biology with respect to conservation of biological diversity can result from direct and indirect, intended or unintended, as well as immediate or delayed effects. These effects may occur at the genetic, population, or ecosystem level.

65. On this basis, the following examples of potential adverse effects or risks were identified:

(a) An engineered fitness advantage may lead to invasiveness;

(b) Enhanced gene flow that leads to loss of biodiversity;

(c) An increased pathogenic potential;

(d) Increased levels of toxic substances, which may lead to disruptive effects on soil, food-webs, and pollinators;

(e) Negative effects on non-target organisms such as pollinators;

(f) Changes in organisms on the level of basic metabolic pathways, such as altered photosynthesis pathways, carbohydrate metabolism or nitrogen fixation, which, among other effects, may lead to changes in agricultural practice and land-use and may challenge risk assessment.

(g) Applications which aim to alter and replace natural populations (e.g. gene drives) may have adverse effects at an ecosystem level.

Objective 2: Sustainable use of biological diversity

[9] The AHTEG agreed that "potential adverse effects" rather than "risk" would be used in this context in line with the language of the Cartagena Protocol.

66. On this basis, the following examples of potential adverse effects or ~~risks~~ were mentioned:

(a) An increased demand for biomass crops, as well as changes in extraction patterns of biomass and other sources of energy, may lead to an ~~increase in the area of arable land;~~

(b) Replacement of natural products may lead to changes in agricultural practices of communities, which may displace traditional crops, practices and livelihoods;

(c) ~~Effects on agrobiodiversity due to gene flow;~~

(d) Applications which aim to alter and replace natural populations (e.g. gene drives) may have adverse effects at an ecosystem level

Objective 3: Equitable sharing of the benefits of biological diversity

67. Provisions on the Fair and equitable sharing of benefits from the use of biological diversity is addressed by Articles 15 and 16 of the Convention and the Nagoya Protocol. ~~Specific potential risks~~ and adverse effects resulting from synthetic biology may be as follows:

(a) Loss of market share and income by indigenous and local communities due to the altered exploitation of genetic resources

(b) Shift in the understanding of what constitutes a genetic resource and implications thereof, e.g. the misappropriation of the original source of the DNA information, and consequently if benefits are derived from the use of such DNA information, without prior informed consent and mutually agreed terms, the fair and equitable sharing of the benefits would not be possible.

(c) ~~Evasion~~ of access and benefit sharing ~~obligations~~ through the use of sequenced data ~~resulting in avoidance of execution of the material transfer agreements under the Nagoya Protocol;~~

(d) Patent driven and open-source approaches to synthetic biology may have different implications in the context of access and benefit sharing.

(e) Indigenous peoples and local communities will not necessarily share the benefits of synthetic biology.

3.6. Best practices on risk assessment and monitoring regimes currently used by Parties to the Convention and other Governments

68. Under this agenda item, members of the AHTEG considered whether additional efforts are needed to compile information on best practices, taking into account the previous work of the best practices identified in the submissions of information[10] and online discussions[11], and the ways forward with regard to facilitating the sharing, dissemination and use of this information by Parties and other Governments.

69. The AHTEG noted that the best practices submitted are primarily based on experiences with LMO risk assessment within the context of Annex 3 of the Cartagena Protocol.

70. Members of the AHTEG concluded that it would be useful to compile the existing body of knowledge on relevant best practices on risk assessment and monitoring in a single and easily accessible online portal under, for example, the Biosafety-Clearing House of the Cartagena Protocol or the Clearing-House Mechanism of the Convention.

71. With regards to additional topics on which best practices may need to be complied, members of the AHTEG noted that best practices on the standardization of risk assessment methodologies, as well as on monitoring are under-represented and an invitation for submissions of these topics would be useful.

3.7. Degree to which the existing arrangements constitute a comprehensive framework in order to address impacts of organisms, components and products resulting from synthetic biology, in particular threats of significant reduction or loss of biological diversity

72. Under this agenda item, the AHTEG considered that a comprehensive framework would include arrangements that address the impacts of organisms, components and products of synthetic biology in the context of the three objectives of the Convention, in line with article 8(g) and decision XII/24.

73. In considering the degree to which existing risk assessment principles and methodologies constitute a comprehensive framework to address the impact of synthetic biology organisms, some members of the Group noted that risk assessment practices currently in place to evaluate LMOs are sufficient and appropriate to evaluate organisms of synthetic biology, and may be modified to accommodate new specific considerations of synthetic biology if and when the need arises.

74. Some members, however, noted that current risk assessment approaches and methodologies must be adapted to address matters that are of particular relevance to synthetic biology. These members identified the lack of familiarity in comparison to non-modified organisms, challenges in establishing meaningful comparators, and possibly higher levels of uncertainty as gaps in the existing methodologies for assessing the environmental impacts of synthetic biology organisms, and identified a need for guidelines and capacity building to be developed and made available.

75. The views of the members of the AHTEG diverged with regard to whether or not current methodologies to address environmental impacts of the components and products of synthetic biology are adequate or even needed.

76. With regard to the socio-economic considerations of the impacts of synthetic biology on the three objectives of the Convention, some members of the Group noted that this is not sufficiently addressed by existing frameworks.

77. With regard to the fair and equitable sharing of the benefits of synthetic biology, some members of the AHTEG noted that there is no comprehensive framework to assess the added-value of synthetic biology applications to society nor methodologies to integrate ethical values that are relevant to society.

78. The need for coordination with current processes under the Cartagena Protocol on Biosafety was noted, in particular with the AHTEG on Socio-economic Considerations and the AHTEG on Risk Assessment and Risk Management.

79. Some members of the AHTEG noted that the existing arrangements to address the impacts of ~~organisms,~~ components and products resulting from synthetic biology are fragmented and do not constitute a comprehensive framework.

[10] Available at http://www.cbd.int/doc/notifications/2015/ntf-2015-013-synthetic-biology-en.pdf.

[11] Available at http://bch.cbd.int/synbio/open-ended/discussion.shtml.

ITEM4. CONCLUSIONS AND WAYS FORWARD, INCLUDING ELEMENTS TO FACILITATE FUTURE DISCUSSIONS AND ACTIONS ON SYNTHETIC BIOLOGY UNDER THE CONVENTION

80. Reaffirming decision XII/24 to urge Parties and invite other Governments to take a precautionary approach, in accordance with paragraph 4 of decision XI/11, the AHTEG, having deliberated on the tasks mandated by the COP, makes the following proposals on the ways forward for future actions on Synthetic Biology for consideration by the SBSTTA in its recommendations to COP to:

(a) Establish a process to monitor and assess the state of knowledge within the field of synthetic biology on a regular basis, review new information regarding the positive and negative impacts of synthetic biology on the three objectives of the Convention, and update the proposed operational definition as appropriate.

(b) Urge Parties to address synthetic biology in a coordinated manner with the context of the objectives of the Convention and its Protocols, particularly tapping into existing processes such as the AHTEG on Risk Assessment and Risk Management and the AHTEG on Socio-economic Considerations under the Cartagena Protocol.

(c) Promote the use of online tools to facilitate the work on synthetic biology in the context of the Convention and its Protocols.

(d) Coordinate and establish synergies with other UN and international organizations, whose mandates are relevant to synthetic biology including Codex Alimentarius, WIPO, OIE, TRIPS and UNIDO, amongst others.

(e) Create or expand on existing online platforms to facilitate knowledge and information sharing on risk assessment research, positive and negative impacts of synthetic biology, *inter alia*, through the Biosafety-Clearing House or the Clearing-House Mechanism.

(f) Promote capacity building and encourage cooperation among Parties, other governments and relevant organizations.

(g) Invite the Conference of the Parties serving as the meeting of the Parties to the Nagoya Protocol to set up mechanisms to clarify the issue of digital genetic resource information as it relates to access and benefit sharing.

(h) Assess potential gaps in oversight under the Convention and its Protocols with regard to the components and products of synthetic biology.

(i) Urge the Convention to promote the full engagement of indigenous people and local communities in future activities relating to synthetic biology.

(j) Promote engagement among Parties, other Governments and relevant stakeholders to discuss, inter alia, the potential benefits and potential adverse effects of synthetic biology, development of guidelines, public awareness, communication and education, and ethical considerations in the context of the three objectives of the Convention.

ITEM 5. OTHER MATTERS

81. There were no other matters raised by the Group.

ITEM 6. ADOPTION OF THE REPORT

82. The draft report was introduced to the Group by the Rapporteur. The Chair invited the Group to consider the report, which was adopted as amended.

ITEM 7. CLOSURE OF THE MEETING

83. The meeting was closed on f Friday, 25 September 2015 at XX:XX.

From: Jaimie Schnell
To: Cecile Girard; Dylan Levac; Jaimie Schnell; NHQ-AC_Skyline_T1-0-217; ...
Date: 2015-11-05
Time: 11:00 AM - 12:00 PM
Subject: Gene drive webinar
Place: NHQ-AC_Skyline_T1-0-217

Hi all,

I've registered for the NAS webinar on Key Principles and Considerations for Risk Assessment of Gene Drive Research and Applications (http://nas-sites.org/gene-drives/2015/10/04/webinar-risk-assessment/)

I'll bring my computer and set up to watch it in T1-0-217 if anyone wants to join me :)

From: Jaimie Schnell
Date: 2015-11-05
Time: 11:00 AM - 12:00 PM
Subject: Gene Drive Webinar

From: Jaimie Schnell
Date: 2015-11-19
Time: 10:00 AM - 11:45 AM
Subject: Gene Drive Webinar

From:
Sent: 2015-11-19 4:08:20 AM
To:
Jaimie.Schnell@inspection.gc.ca;

CC:
BCC:
Subject: ISBGMO14 - a tentative programme to trigger reactions

Dear ISBGMO14 scientific programme committee members,
Hi all,

It has been a while since you got bombarded by ISBGMO14-related eMails. Since an ISBR board conference call is scheduled in DEC somewhere, it is time to break the silence and translate the time of reflection into another set of valuable and concrete suggestions.

Building on the helpful thoughts exchanged so far and following a suggestion from I prepared the attached tentative scientific programme, consisting of:

- 3 plenary sessions (looking at the past, the present, and ahead)
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To ease our discussion, titles for sessions and talks are given, as well as potential session organisers and speakers. At this stage, most of the information is tentative/speculative, but it gives you a good indication of the progress made so far, and where we are heading to. I therefore would be very grateful if you could play the game, and share your thoughts on the draft proposal. Feel free to use track changes to revise the proposal.

I am fully aware it is too early to fix the programme and that flexibility should be ensured to allow the inclusion of "hot" issues that may arise in 2016. You will see that several slots are left open for this reason. Yet, our exercise may help us identify speakers we really would like to have on board, allowing us to approach them early in the process.

I must admit I am ignorant in the field of synthetic biology, so any feedback on this matter would be most welcomed.

Many thanks in advance,

<<File: TEXT.htm>>
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PRELIMINARY DOCUMENT DESIGNED TO INITIATE FURTHER DISCUSSION

14th INTERNATIONAL SYMPOSIUM ON THE BIOSAFETY OF GENETICALLY MODIFIED ORGANISMS (ISBGMO14)

(Guadalajara, Mexico, March 2017)

	Monday, xx March MORNING		
	Welcome addresses -LOC -President of ISBR -Student Awards		
	Latin American delegate **Name**, *affiliation*		
	Plenary Session I: Advancing ERA of GM plants – The Past *Organizers:* **Name**, *affiliation* *(expression of interest: xxx)*		
Keynote	Overview of ERA questions posed when the first generation of GM plants reached the market **Phil McDonald**, *affiliation*		
	Experience gained on potential impacts of vertical gene flow *affiliation*		
	Experience gained on potential resistance evolution in target insect pests *affiliation*		
	COFFEE BREAK		
	Experience gained on potential impacts on non-target organisms and the ecosystem services they contribute to (covering terrestrial, soil and aquatic organisms) , *affiliation*		
	Experience gained on the assessment of potential unintended effects **Jaimie Schnell**, *affiliation*		
	Experience gained on potential impacts on food/feed safety , *affiliation*		
	Panel discussion **Name**, *affiliation* (moderator)		
	LUNCH		
	AFTERNOON		
	Parallel Session I **Vertical gene flow between GM plants and sexually compatible relatives – dangerous liaisons or business as usual?** Organizers: ***Name, Affiliation***	**Parallel Session II** **Tiered approach fit for purpose to inform the NTO risk assessment of GM plants** Organizers: ***Name, Affiliation***	**Parallel Session III** **Types of evidence and efforts necessary to inform the safety assessment of unintended changes/traits in GM plants (Jaimie)** Organizers: ***Name, Affiliation***
	xxx , *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	COFFEE BREAK		
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx	Xxx	Xxx

	Name, *affiliation*	**Name**, *affiliation*	**Name**, *affiliation*
	Poster Session I		
	Xxx		
	Xxx		
	Xxx		
	Xxx		

Tuesday, xx March MORNING			
Plenary Session II: Advancing ERA of GM plants – The Present *Organizers:* **Name**, *affiliation* *(expression of interest: xxx)*			
	Data harmonisation across jurisdictions **Name**, *affiliation*		
	Data relevance – problem formulation **Name**, *affiliation*		
	Data reliability – quality standards **Name**, *affiliation*		
	COFFEE BREAK		
	Data transportability **Name**, *affiliation*		
	Proportionality of data requirements **Name**, *affiliation*		
	Protection goals and environmental harm **Name**, *affiliation*		
	Panel discussion **Name**, *affiliation* (moderator)		
	LUNCH		
AFTERNOON			
	Parallel Session IV **Harmonisation and transportability of risk assessment data – criteria to assess the transportability of ERA data and ERAs performed in other jurisdictions** Organizers: ***Name,*** *Affiliation*	**Parallel Session V** **ERA vs. ecological research – the relevance of a good problem formulation to ensure that gathered data are useful for ERA (organiser tbc)** Organizers: ***Name,*** *Affiliation*	**Parallel Session VI** **xxx** Organizers: ***Name,*** *Affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	COFFEE BREAK		
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Panel discussion **Name**, *affiliation* (moderator)	Panel discussion **Name**, *affiliation* (moderator)	Panel discussion **Name**, *affiliation* (moderator)
	Poster Session II		
	Xxx		
	Xxx		
	Xxx		
	Xxx		
	Pecha Kucha Evening Session (dedicated to young researchers who are offered the opportunity to briefly present their on-going research activities)		
	Xxx		
	Xxx		
	Xxx		
	Xxx		

Wednesday, xx March MORNING			
	Parallel Session VII **Synthetic biology (organiser tbc)** Organizers: ***Name***, *Affiliation*	**Parallel Session VIII** **Ecosystem services concept in the frame ERA of GMOs (and other stressors)** Organizers: ***Name***, *Affiliation*	**Parallel Session IX** Organizers: ***Name***, *Affiliation* **(Submitted presentations)**
	Xxx **Name**, *affiliation*	Protection goals, environmental harm and ecosystem services *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Ecosystem services concept to make protection goals operational and define environmental harm **Name**, *EFSA representative*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Ecosystem services as assessment endpoints *US EPA*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Interrelationship between ecosystem services and biodiversity **Name**, *affiliation*	Xxx **Name**, *affiliation*
	COFFEE BREAK		
	Xxx **Name**, *affiliation*	Trade-offs between protection goals **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Integrating the assessment of multiple stressors in ERA **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	LUNCH		
AFTERNOON			
	SOCIAL PROGRAM		

Thursday, xx March MORNING			
	Plenary Session III: Advancing ERA of GM plants – The Future *Organizers:* **Name**, *affiliation* *(expression of interest: xxx)*		
Keynote	ERA of GM plants – challenges ahead (sustainability of ecosystems, food security, climate change, innovation) *affiliation*		
	GM trees **Name**, *affiliation*		
	GM grasses **Name**, *affiliation*		
	COFFEE BREAK		
	Output traits **Name**, *affiliation*		
	New plant biotechnology-based breeding techniques I – opportunities **Name**, *affiliation*		
	New plant biotechnology-based breeding techniques II – challenges (genome editing / gene drive technology) **Name**, *affiliation*		
	Panel discussion **Name**, *affiliation* (moderator)		
	LUNCH		
	AFTERNOON		
	Parallel Session X **ERA considerations for RNAi-based GM plants – differences/similarities with GM plants expressing novel proteins** Organizers: ***Name****, Affiliation*	**Parallel Session XI** **ERA considerations for GM insects** Organizers: ***Name****, Affiliation*	**Parallel Session XII** Organizers: ***Name****, Affiliation* **(Submitted presentations)**
	NTO testing under laboratory conditions *affiliation*	Overview of applications/technologies (development pipeline) *Intrexon/Oxitec*	Xxx **Name**, *affiliation*
	NTO testing under laboratory and field conditions *affiliation*	Overview of ERA guidelines **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Transfer of dsRNA to higher trophic levels *affiliation*	ERA studies **Name**, *affiliation*	Xxx **Name**, *affiliation*
	COFFEE BREAK		
	eRNAi in arthropods or Fate of dsRNA in the soil *affiliation*	Gene drive overdrive **Name**, *affiliation*	Xxx **Name**, *affiliation*
	US EPA white paper **Name**, *affiliation*	UK Parliament & House of Lords inquiries **Name**, *affiliation*	Xxx **Name**, *affiliation*
	eRNAi in vertebrates *affiliation*	Weighing risks and benefits **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Panel discussion **Name**, *affiliation* (moderator)	Panel discussion **Name**, *affiliation* (moderator)	Panel discussion **Name**, *affiliation* (moderator)
	CLOSING SESSION		

From:
Sent: 2015-11-24 3:32:15 PM
To:
Jaimie.Schnell@inspection.gc.ca;

CC:
BCC:
Subject: RE: ISBGMO14 - a tentative programme to trigger reactions

Some quick thoughts before I head out

1. Excellent start.

2. I can work on some thoughts about the Synthetic Biology topic. Some initial thoughts.

a. One presentation would define and introduce the topic, tools, etc.

b. A second presentation would describe potential products of the future.

c. One presentation could be on how SynBio might fit into the Cartegena Protocol or other regulatory schemes. For example, in the Cart Prot we shift from actually moving living organisms in vials or pots to moving genetic codes via email to labs where new organisms can be produced.

d. And then there is a discussion about risk assessment – hazard, exposure, etc. If you develop a novel organism with fully synthetic genes, what are the appropriate comparators?

e. ISBGMO in the past has dealt mostly with crop plants, a few trees and grasses, and an occasional insect. But why? Why not GM mammals or other higher organisms? Why not GM simple plants or other single celled organisms?

f. (Did I mention the North Face "Moon Parka" jacket that will go on sale in 2016 – the shell is made out of woven spider silk trademark "Qmonos" produced by the Spiber company.)

3. The last plenary – why just plants? I look at the recent activity for GM salmon and the Oxitec work with mosquitoes and lepidoptera, and I see some really neat non-plant things on the not so distant horizon.

4. I really like the idea of bringing in sustainability, food security, climate change, etc. I would actually propose using these as the major topics in the "future" discussion rather than NBT. Somehow it seems to me that finishing the meeting with a highly technical topic such as NBT isn't as "visionary" as a discussion about how we are going to feed 9 billion people in a sustainable manner. Technically interesting, but may not arouse the "this is a great time to be a risk assessor" emotions of meeting participants.

5. So I would consider splitting a parallel session to include NBT and SynBio. Start with NBT (currently bearing fruit) and move to SynBio (promise of tomorrow).

I'll dig deeper when I get back to the office

From:
Sent: Thursday, November 19, 2015 3:08 AM

To:

Jaimie Schnell'

Cc: '

Subject: ISBGMO14 - a tentative programme to trigger reactions

Dear ISBGMO14 scientific programme committee members,
Hi all,

It has been a while since you got bombarded by ISBGMO14-related eMails. Since an ISBR board conference call is scheduled in DEC somewhere, it is time to break the silence and translate the time of reflection into another set of valuable and concrete suggestions.

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I must admit I am ignorant in the field of synthetic biology, so any feedback on this matter would be most welcomed.

Many thanks in advance,

Francais Deutsch Italiano Espanol Portugues Japanese Chinese Korean

http://www.DuPont.com/corp/email_disclaimer.html
<<File: TEXT.htm>>
<<File: Mime.822>>

From:
Sent: 2015-12-21 2:20:08 PM
To:
Jaimie.Schnell@inspection.gc.ca;

CC:
BCC:
Subject: RE: ISBGMO14 - a tentative programme to trigger reactions

Dear
Thank you for sharing the tentative programme.
We had the meeting of the Local Committee a few days ago and I am ready to share with you some initial reactions from the members, for your consideration and feedback.
We will keep working on some more issues (possible speakers, organizers, presentations tittles etc) but for now I hope this is useful.
Kind regards and best wishes

De: |
Enviado el: jueves, 19 de noviembre de 2015 03:08 a. m.
Para: |
'Jaimie Schnell'
CC:
Asunto: ISBGMO14 - a tentative programme to trigger reactions

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<<File: DRAFT_Program_2015_11_19_sesionComments LOC V2.docx>>
<<File: Mime.822>>

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	COFFEE BREAK		
	Experience gained on potential impacts on non-target organisms and the ecosystem services they contribute to (covering terrestrial, soil and aquatic organisms) *affiliation*		
	Experience gained on the assessment of potential unintended effects **Jaimie Schnell**, *affiliation*		
	Experience gained on potential impacts on food/feed safety *affiliation*		
	Panel discussion **Name**, *affiliation* (moderator)		
	LUNCH		
	AFTERNOON		
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	xxx *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Gene Flow between GM corn and: conventional corn *Tripsacum*, and Teocintle. ~~Xxx~~ ~~**Name**, *affiliation*~~	Xxx **Name**, *affiliation*	Xxx **Name** *Department of Animal Science, University of California, Davis* ~~*95616affiliation*~~
	~~Xxx~~ **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	COFFEE BREAK		
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx	Xxx	Xxx

Comment : Could you share with us what this figure of Latin American delegate means?

Comment : Is this suggestion to elaborate a sharp sentence of the basic question, the academic imperative or the productive/ regulatrory challenge?

Comment Consider if the time will be enouhg for the number of participants.

Comment : Could this talk touch also on persistance and invasivness?

Comment Is this covering all kind of GMOs (mosquitoes, other insects, fish, bacteial inoculants)?
→*see Parallel Session III*

Comment : This could include other corporate investigators of actual Bt events

Comment We propose in relation to ther paper: **Prevalence and impacts of genetically engineered feedstuffs on livestock populations, 2014.**

Comment | from ITESM-Monterrey who works in basic and applied projects in maize. He is the author of a recent publication on the subject.

	Name, *affiliation*	**Name**, *affiliation*	**Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Poster Session I		
	Xxx		
	Xxx		
	Xxx		
	Xxx		

Tuesday, xx March MORNING			
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	COFFEE BREAK		
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	Panel discussion **Name**, *affiliation* (moderator)		
	LUNCH		
AFTERNOON			
	Parallel Session IV **Harmonisation and transportability of risk assessment data – criteria to assess the transportability of ERA data and ERAs performed in other jurisdictions** Organizers: ***Name,*** *Affiliation*	**Parallel Session V** **ERA vs. ecological research – the relevance of a good problem formulation to ensure that gathered data are useful for ERA (organiser tbc)** Organizers: ***Name,*** *Affiliation*	**Parallel Session VI** ~~xxx~~Contributions (actual and potential) of Biotech crops to to sustainable agriculture and adaptation to Climate Change Organizers: ***Name,*** *Affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation Productive Mexican scientists in this line, could participate*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx ~~Name~~, CGIAR Independent Science and Partnership Council Secretariat~~affiliation~~
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx ~~Name~~, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	COFFEE BREAK		
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	~~Xxx~~GE plants and Bioremediation Department of Biology (B/M219) University of York,United Kingdom ~~Name, affiliation~~
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Panel discussion	Panel discussion	Panel discussion

Comment : In the final context (all is risky), here the comparison or balance with benefits must be included (as a formal scheme or strategy)

Comment : This proposed session could correspond to the section on Protection goals. Also to review how GMO could contribuite to mitiagate effects of CC, in the big context since COP21 and MOP8-PCB 3 months before...

Comment : We expect some regulators interested in update normatives, may participate.

Comment : Could be him or other of the authours of the paper: „Green Revolution research saved an estimated 18 to 27 million hectares from being brought into agricultural production". PNAS 2012

Comment : Considering that she may have some actializations on the paper: Impact of GM crops on biodiversity (2011).

Comment : We consider becasue of his area of expertise. Examples of publications on the topic:
Monodehydroascorbate reductase mediates TNT toxicity in plants; Johnston, E. J., Rylott, E. L., Beynon, E., Lorenz, A., Chechik, V. & Bruce, N. C. 4 Sep 2015
Article in Science (New York, N.Y.)
Arabidopsis Glutathione Transferases U24 and U25 Exhibit a Range of Detoxification Activities with the Environmental Pollutant and Explosive, 2,4,6-Trinitrotoluene; Gunning, V., Tzafestas, K., Sparrow, H., Johnston, E. J., Brentnall, A. S., Potts, J. R., Rylott, E. L. & Bruce, N. C. 14 Apr 2014
Article in Plant Physiology

	Name, *affiliation* (moderator)	**Name**, *affiliation* (moderator)	**Name**, *affiliation* (moderator)
	Poster Session II		
	Xxx		
	Xxx		
	Xxx		
	Xxx		
	Pecha Kucha Evening Session (dedicated to young researchers who are offered the opportunity to briefly present their on-going research activities)		
	Xxx		
	Xxx		
	Xxx		
	Xxx		

Wednesday, xx March MORNING			
	Parallel Session VII **Synthetic biology (organiser tbc)** Organizers: ***Name**, Affiliation*	**Parallel Session VIII** **Ecosystem services concept in the frame ERA of GMOs (and other stressors)** Organizers: ***Name**, Affiliation*	**Parallel Session IX** Latin American Session Organizers: ***Name**, Affiliation* **(Submitted presentations)**
	Xxx **Name**, *affiliation*	Protection goals, environmental harm and ecosystem services *affiliation*	~~Xxx~~Argentina´s experience on the regulated use of GM crops ~~Name~~ ~~*affiliation*~~*CONABIA?*
	Xxx **Name**, *affiliation*	Ecosystem services concept to make protection goals operational and define environmental harm **Name**, *EFSA representative*	~~Xxx~~The work of ICCA and the status of Central American countries on biosafety ~~Name~~ ~~*affiliation*~~*IICA*
	Xxx **Name**, *affiliation*	Ecosystem services as assessment endpoints *US EPA*	Xxx **Name**, ~~*affiliation*~~*Ecuador?*
	Xxx **Name**, *affiliation*	Interrelationship between ecosystem services and biodiversity **Name**, *affiliation*	Brazil´s experience on the regulated use of GM crops~~Xxx~~ ~~Name~~, (CIB-Brasil) or research leaders from ~~enoni~~, ~~*affiliation*~~*Embrapa*
	COFFEE BREAK		
	Xxx **Name**, *affiliation*	Trade-offs between protection goals **Name**, *affiliation*	Other LatAm countries (Uru, Par, Bol, Col)~~Xxx~~ ~~Name~~ (ArgenBio-ASA) or conctacs through her)~~ytes, *affiliation*~~
	Xxx **Name**, *affiliation*	Integrating the assessment of multiple stressors in ERA **Name**, *affiliation*	~~Xxx~~Researchers, entrpreneurship and Spin-off experiences ~~Name~~ Langebio-CINVESTAV,Stela Genomics ~~*affiliation*~~
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	~~Xxx~~ Biosafety research, regulatory development and judicial conflicts, Cibiogem **Name**, *affiliation*
	LUNCH		
AFTERNOON			
	SOCIAL PROGRAM **Field Trip and Dinner**		

Comment The Local committe would like to propose a Session on Latin American issues on biosafety, adoption, chalenges and opportunities

Thursday, xx March MORNING			
	Plenary Session III: Advancing ERA of GM plants – The Future *Organizers:* **Name**, *affiliation* *(expression of interest: xxx)*		
Keynote	ERA of GM plants – challenges ahead (sustainability of ecosystems, food security, climate change, innovation) *affiliation*		
	GM trees **Name** *affiliation*Oregon State University (Embrapa -- Eucalyptus; ' EcoSur-endangered tropical wooden species)		
	GM grasses **Name**, *affiliation*		
	COFFEE BREAK		
	Output traits **Name**, *affiliation*		
	New plant biotechnology-based breeding techniques I – opportunities **Name**, *affiliation*		
	New plant biotechnology-based breeding techniques II – challenges (genome editing / gene drive technology) **Name**, *affiliation*		
	Panel discussion **Name**, *affiliation* (moderator)		
	LUNCH		
AFTERNOON			
	Parallel Session X **ERA considerations for RNAi-based GM plants – differences/similarities with GM plants expressing novel proteins** Organizers: ***Name, Affiliation***	**Parallel Session XI** **ERA considerations for GM insects** Organizers: ***Name, Affiliation***	**Parallel Session XII** ERA considerations for CRISPR- CAS-9 differences/ similarities with GM plants Organizers: ***Name, Affiliation*** **(Submitted presentations)**
	NTO testing under laboratory conditions *affiliation*	Overview of applications/technologies (development pipeline) *Intrexon/Oxitec*	~~Xxx~~New **Name**, *affiliation*
	NTO testing under laboratory and field conditions *affiliation*	Overview of ERA guidelines **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Transfer of dsRNA to higher trophic levels *affiliation*	ERA studies **Name**, *affiliation*	Xxx **Name**, *affiliation*
	COFFEE BREAK		
	eRNAi in arthropods or Fate of dsRNA in the soil *affiliation*	Gene drive overdrive **Name**, *affiliation* *NCSU-US*	Xxx **Name**, *affiliation*
	US EPA white paper **Name**, *affiliation*	UK Parliament & House of Lords inquiries **Name**, *affiliation*	Xxx **Name**, *affiliation*
	eRNAi in vertebrates *affiliation*	Weighing risks and benefits **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Panel discussion **Name**, *affiliation* (moderator)	Panel discussion **Name**, *affiliation* (moderator)	Panel discussion **Name**, *affiliation* (moderator)
	CLOSING SESSION		

Commen: This is another proposal to start looking at the applications of CRISPR and how the ERA could work. In 2017 some R&D in crops could be advanced enough

s.19(1)

From: Sarah G. Davis
To: Schnell, Jaimie
Date: 2016-01-04 4:25 PM
Subject: Fwd: RE: ISBGMO14 - a tentative programme to trigger reactions

Hi Jaimie,

Happy New Year to you as well. Were you able to take some time off last week?

Thanks for keeping me in the loop with regards to the ISBGMO emails. I keep meaning to delve into the agenda more deeply and offer my two cents' worth. I'll try and make it my New Year's resolution. :)

I hope all is well,
Sarah

>>> Jaimie Schnell 2016-01-04 12:39 PM >>>
Hi Sarah,

Happy New Year! Here is another ISBGMO related email.

Jaimie

>>> ' > 2016-01-04 12:11 PM >>>

and Group

Happy New Year - hope you all had a restful holiday break.

I like the latest round of comments and have added a few more on top of the version that sent out (see attached document).

Some general thoughts:

1. Looking backwards I think we have been planting enough crops in certain areas that we should be able to ask "so what happened?" - a few scenarios come to mind (a) Canada and canola - incredible market penetration... so what has happened environmentally? (b) USA maize and/or soy ... what environmental effects have been seen? What about shifts in pesticide use? (c) Do we want to open a discussion on Monarchs in the USA - unintended consequences of weed control offered by glyphosate tolerant crops? (d) Are there stories for GM cotton in India and/or China in terms of environmental effects? (e) Do we want to bring up landscape level shifts due to adoption of GM crops - shifts is where you can grow certain crops economically due to weed control?

2. A few "hot" topics that keep coming up in the regulatory ERA world in the "present" include: ERA for stacks, ERA for LLP (low level presence in seed), ERA for Low Exposure Scenarios (low levels in imported grain). Are there other "present" topics that should be discussed?

3. I wish we had a parallel session for submitted "short" papers - it would seem to involve more people in the meeting. Yes, the poster sessions are good, but short papers are good too.

4. In looking towards the future it seems that there is an amazing amount of work being done on lots of different crops and organisms. I suggest that we should find a way to bring in the folks doing work on bananas, apples, citrus, sorghum, rice, wheat, alfalfa, potato, jute, fish, etc. I wonder if any crops will

s.19(1)

not have GM versions within 10 years. So much of our ERA discussion seems to be maize centric, but some of the more challenging ERA's might in some of these "smaller" or "local" crops where not much previous ERA work has been done.

5. I like the increased attention being given to food/feed safety. I have long argued that food/feed safety is a topic that could be part of ISBGMO. Perhaps rather than a sporadic mention in a few talks it deserves a separate session on not just the "unintended effects" or "food/feed safety" but also a discussion on how food/feed risk assessment is conducted around the world (could include some thoughts on harmonization).

6. I suggest that we take all of the new breeding technology, CRISPR/CAS, and SynBio and put it into a single technical session. Then have a summary presentation in the final plenary session. That way the in-depth technical material is covered in one place for those interested in the details, and the "this is how ERA principles can be applied to new technologies" is in another place for the general audience for all to hear.

I think that the Synthetic Biology presentation would be (a) this is what SynBio is, (b) this is what types of "products" we might see in the future, and (c) this is how ERA principles can apply. One could expand the discussion to how it fits into the Cartegena Protocol process... While I believe that ISBGMO is the logical local to discuss "ERA and SynBio" I am not sure if the topic is far enough along to warrant an entire session.

Thanks.

From:
Sent: Monday, December 21, 2015 1:20 PM
To:
'Jaimie Schnell'
Cc:
Subject: RE: ISBGMO14 - a tentative programme to trigger reactions

Dear
Thank you for sharing the tentative programme.
We had the meeting of the Local Committee a few days ago and I am ready to share with you some initial reactions from the members, for your consideration and feedback.
We will keep working on some more issues (possible speakers, organizers, presentations tittles etc) but for now I hope this is useful.
Kind regards and best wishes

De:
Enviado el: jueves, 19 de noviembre de 2015 03:08 a. m.
Para:
'Jaimie Schnell'
CC:
Asunto: ISBGMO14 - a tentative programme to trigger reactions

s.19(1)

Dear ISBGMO14 scientific programme committee members,
Hi all,

It has been a while since you got bombarded by ISBGMO14-related eMails. Since an ISBR board conference call is scheduled in DEC somewhere, it is time to break the silence and translate the time of reflection into another set of valuable and concrete suggestions.

Building on the helpful thoughts exchanged so far and following a suggestion from Sol/Ariel, I prepared the attached tentative scientific programme, consisting of:

- 3 plenary sessions (looking at the past, the present, and ahead)
- 12 parallel/break-out sessions (which zoom into a subset of the issues discussed at the plenary sessions)
- Pecha Kucha evening session
- Social event - afternoon with dinner

To ease our discussion, titles for sessions and talks are given, as well as potential session organisers and speakers. At this stage, most of the information is tentative/speculative, but it gives you a good indication of the progress made so far, and where we are heading to. I therefore would be very grateful if you could play the game, and share your thoughts on the draft proposal. Feel free to use track changes to revise the proposal.

I am fully aware it is too early to fix the programme and that flexibility should be ensured to allow the inclusion of "hot" issues that may arise in 2016. You will see that several slots are left open for this reason. Yet, our exercise may help us identify speakers we really would like to have on board, allowing us to approach them early in the process.

I must admit I am ignorant in the field of synthetic biology, so any feedback on this matter would be most welcomed.

Many thanks in advance,

From:
Sent: 2016-01-04 12:11:57 PM
To:
Jaimie.Schnell@inspection.gc.ca;

CC:
BCC:
Subject: RE: ISBGMO14 - a tentative programme to trigger reactions

and Group

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Many thanks in advance,

<<File: TEXT.htm>>
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PRELIMINARY DOCUMENT DESIGNED TO INITIATE FURTHER DISCUSSION

14th INTERNATIONAL SYMPOSIUM ON THE BIOSAFETY OF GENETICALLY MODIFIED ORGANISMS (ISBGMO14)

(Guadalajara, Méexico, March 2017)

Monday, xx March MORNING			
	Welcome addresses -LOC -President of ISBR -Student Awards		
	Latin American delegate **Name**, *affiliation*		
	Plenary Session I: Advancing ERA of GM plants – The Past *Organizers:* **Name**, *affiliation* *(expression of interest: xxx)*		
Keynote	Overview of ERA questions posed when the first generation of GM plants reached the market **Phil McDonald**, *affiliation*		
	Experience gained on potential impacts of vertical gene flow *affiliation*		
	Experience gained on potential resistance evolution in target insect pests *affiliation*		
	COFFEE BREAK		
	Experience gained on potential impacts on non-target organisms and the ecosystem services they contribute to (covering terrestrial, soil and aquatic organisms) *affiliation*		
	Experience gained on the assessment of potential unintended effects **Jaimie Schnell**, *affiliation*		
	Experience gained on ~~potential impacts on~~on the assessment of food/feed safety *affiliation*		
	Panel discussion **Name**, *affiliation* (moderator)		
	LUNCH		
AFTERNOON			
	Parallel Session I **Vertical gene flow between GM plants and sexually compatible relatives – dangerous liaisons or business as usual?** Organizers: ***Name, Affiliation***	**Parallel Session II** **Tiered approach fit for purpose to inform the NTO risk assessment of GM plants** Organizers: ***Name, Affiliation***	**Parallel Session III** **Types of evidence and efforts necessary to inform the safety assessment of unintended changes/traits in GM plants** Organizers: ***Name, Affiliation***
	xxx *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Gene Flow between GM corn and: conventional corn *Tripsacum*, and Teocintle. ~~Xxx~~ ~~**Name**, *affiliation*~~	Xxx **Name**, *affiliation*	Xxx **Name** *Department of Animal Science; University of California, Davis 95616*~~*affiliation*~~
	~~Xxx~~ **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	COFFEE BREAK		
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx	Xxx	Xxx

Comment : My suggestion would be someone relatively high up in the government or science arena who can say „Welcome to our country [region] and not lets talk about science."

Comment : Could you share with us what this figure of Latin American delegate means?

Comment : Suggest that „learning from the past" or „Applying past learning to future risk assessments" might focus the session.

Comment : Is this suggestion to elaborate a sharp sentence of the basic question, the academic imperative or the productive/ regulatrory challenge?

Comment : Consider if the time will be enouhg for the number of participants.

Comment : Could this talk touch also on persistance and invasivness?

Comment : I am never very excited about including resistance management in a „biosafety" discussion – unless it is presented in the broader „pest control" context. In general resistance seems to be more of an economic or social issue rather than a safety issue.

Comment : How to focus this on the plant – not ecology?

Comment : Is this covering all kind of GMOs (mosquitoes, other insects, fish, bacteial inoculants)? →*see Parallel Session III*

Comment : This could include other corporate investigators of actual Bt events

Comment : We propose Allison in relation to ther paper: **Prevalence and impacts of genetically engineered feedstuffs on livestock populations, 2014.**

Comment :

Comment : I wonder if there is a way to bring in someone to discuss geneflow between conventional hybrids and Teocintle, land races, etc. to give some context to the GM crop discussion? Also, should we bring in other crops?

	Name, *affiliation*	**Name**, *affiliation*	**Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Poster Session I		
	Xxx		
	Xxx		
	Xxx		
	Xxx		

Tuesday, xx March MORNING			
Plenary Session II: Advancing ERA of GM plants – The Present *Organizers:* **Name**, *affiliation* *(expression of interest: xxx)*			
	Data harmonisation across jurisdictions **Name**, *affiliation*		
	Data relevance – problem formulation **Name**, *affiliation*		
	Data reliability – quality standards **Name**, *affiliation*		
	COFFEE BREAK		
	Data transportability **Name**, *affiliation*		
	Proportionality of data requirements **Name**, *affiliation*		
	Protection goals and environmental harm **Name**, *affiliation*		
	Panel discussion **Name**, *affiliation* (moderator)		
	LUNCH		
AFTERNOON			
	Parallel Session IV **Harmonisation and transportability of risk assessment data – criteria to assess the transportability of ERA data and ERAs performed in other jurisdictions (** Organizers: ***Name, Affiliation***	**Parallel Session V** **ERA vs. ecological research – the relevance of a good problem formulation to ensure that gathered data are useful for ERA (organiser tbc)** Organizers: ***Name, Affiliation***	**Parallel Session VI** ~~xxx~~Contributions (actual and potential) of Biotech crops to to sustainable agriculture and adaptation to Climate Change Organizers: ***Name, Affiliation***
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation Productive Mexican scientists in this line, could participate*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx ~~**Name**~~, CGIAR Independent Science and Partnership Council Secretariat~~affiliation~~
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx ~~**Name**~~, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	COFFEE BREAK		
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	~~Xxx~~GE plants and Bioremediation Department of Biology (B/M219) University of York, United Kingdom ~~**Name**, *affiliation*~~
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Panel discussion	Panel discussion	Panel discussion

Comment | : Three „hot" topics that could be covered here could be (1) ERA for stacks, (2) ERA for LLP (seed low exposure) and (3) ERA for Low Level Exposure (grain imports).

Comment | : Is this data harmonization or harmonization of data requirements, protocols, etc. If I was to approach this I would discuss how we could start with some basic protocol requirements, then move to harmonizing some protocols, then to a list of surrogate organisms, perhaps then a harmonized regional approach (perhaps between a few countries) before moving on to wider harmonization?.

Comment : In the final context (all is risky), here the comparison or balance with benefits must be included (as a formal scheme or strategy)

Comment : Was wondering – are „data" harmonized? Or really do we just harmonize data requirements, protocols, etc. I would leave the „harmonization" for the plenary session and address the detailed transportability discussion in the parallel session.

Comment : This proposed session could correspond to the section on Protection goals. Also to review how GMO could contribuite to mitiagate effects of CC, in the big context since COP21 and MOP8-PCB 3 months before...

Comment | : We expect some regulators interested in update normatives, may participate.

Comment

Comment | : Considering that she may have some actializations on the paper: Impact of GM crops on biodiversity (2011).

Comment We consider becasue of
Examples of publications on the topic:
Monodehydroascorbate reductase mediates TNT toxicity in plants; Johnston, E. J., Rylott, E. L., Beynon, E., Lorenz, A., Chechik, V. & Bruce, N. C. 4 Sep 2015
Article in Science (New York, N.Y.)
Arabidopsis Glutathione Transferases U24 and U25 Exhibit a Range of ... [1]

	Name, *affiliation* (moderator)	**Name**, *affiliation* (moderator)	**Name**, *affiliation* (moderator)
	Poster Session II		
	Xxx		
	Xxx		
	Xxx		
	Xxx		
	Pecha Kucha Evening Session (dedicated to young researchers who are offered the opportunity to briefly present their on-going research activities)		
	Xxx		
	Xxx		
	Xxx		
	Xxx		

Wednesday, xx March MORNING			
	Parallel Session VII **Synthetic biology (organiser tbc)** Organizers: ***Name, Affiliation***	**Parallel Session VIII** **Ecosystem services concept in the frame ERA of GMOs (and other stressors) (Yann)** Organizers: ***Name, Affiliation***	**Parallel Session IX** **Latin American Session** Organizers: ***Name, Affiliation*** **(Submitted presentations)**
	Xxx **Name**, *affiliation*	Protection goals, environmental harm and ecosystem services *affiliation*	~~Xxx~~Argentina´s experience on the regulated use of GM crops ~~**Name**~~ ~~*affiliation*~~*CONABIA?*
	Xxx **Name**, *affiliation*	Ecosystem services concept to make protection goals operational and define environmental harm **Name**, *EFSA representative*	~~Xxx~~The work of ICCA and the status of Central American countries on biosafety ~~**Name**~~ ~~*affiliation*~~*IICA*
	Xxx **Name**, *affiliation*	Ecosystem services as assessment endpoints *US EPA*	Xxx **Name**, ~~*affiliation*~~*Ecuador?*
	Xxx **Name**, *affiliation*	Interrelationship between ecosystem services and biodiversity **Name**, *affiliation*	Brazil´s experience on the regulated use of GM crops~~Xxx~~ ~~**Name**~~, (CIB-Brasil) or research leaders from ~~enoni~~, ~~*affiliation*~~*Embrapa*
	COFFEE BREAK		
	Xxx **Name**, *affiliation*	Trade-offs between protection goals **Name**, *affiliation*	Other LatAm countries (Uru, Par, Bol, Col)~~Xxx~~ ~~**Name**~~ (ArgenBio-ASA) or conctacs through her)~~ytes, *affiliation*~~
	Xxx **Name**, *affiliation*	Integrating the assessment of multiple stressors in ERA **Name**, *affiliation*	~~Xxx~~Researchers, entrpreneurship and Spin-off experiences ~~**Name**~~ Langebio-CINVESTAV,Stela Genomics ~~*affiliation*~~
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	~~Xxx~~ Biosafety research, regulatory development and judicial conflicts, Cibiogem **Name**, *affiliation*
	LUNCH		
AFTERNOON			
	SOCIAL PROGRAM **Field Trip and Dinner**		

Comment | : I would take CRISPR/CAS, other NBT, and SynBio and put them into a single session.

Comment | : The Local committe would like to propose a Session on Latin American issues on biosafety, adoption, chalenges and opportunities

Thursday, xx March MORNING			
	Plenary Session III: Advancing ERA of GM plants – The Future *Organizers:* **Name**, *affiliation* *(expression of interest: xxx)*		
Keynote	ERA of GM plants – challenges ahead (sustainability of ecosystems, food security, climate change, innovation) *affiliation*		
	GM trees ~~Name~~ _____ ~~*affiliation*~~*Oregon State University (Giancarlo Pasquali/ Embrapa -- Eucalyptus; Yuri Peña/ EcoSur-endangered tropical wooden species)*		
	GM grasses **Name**, *affiliation*		
	COFFEE BREAK		
	Output traits **Name**, *affiliation*		
	New plant biotechnology-based breeding techniques I – opportunities **Name**, *affiliation*		
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	Panel discussion **Name**, *affiliation* (moderator)		
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	NTO testing under laboratory conditions *affiliation*	Overview of applications/technologies (development pipeline) *Intrexon/Oxitec*	~~Xxx~~New **Name**, *affiliation*
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	Transfer of dsRNA to higher trophic levels *affiliation*	ERA studies **Name**, *affiliation*	Xxx **Name**, *affiliation*
	COFFEE BREAK		
	eRNAi in arthropods or Fate of dsRNA in the soil *affiliation*	Gene drive overdrive **Name**, *affiliation* *NCSU-US*	Xxx **Name**, *affiliation*
	US EPA white paper **Name**, *affiliation*	UK Parliament & House of Lords inquiries **Name**, *affiliation*	Xxx **Name**, *affiliation*
	eRNAi in vertebrates *affiliation*	Weighing risks and benefits **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Panel discussion **Name**, *affiliation* (moderator)	Panel discussion **Name**, *affiliation* (moderator)	Panel discussion **Name**, *affiliation* (moderator)
	CLOSING SESSION		

Comment | See above – put all new breeding technologies into a single session to discuss the technical details. Then use these time slots to discuss how standard ERA approaches can be applied to deal with future methdologies.

Comment As a „future" session I wonder about organizing a session for new crops and organisms? My gut feeling is that most of the proposed sessions/papers will deal with the standard maize and soy – but what about other GM organisms that are being developed? Rice, sorghum, bananas, wheat, alfalfa, apples, oranges, jute – this is entirely new territory for risk assessors. Oh and fish – gotta talk about fish.

Comment : This is another proposal to start looking at the applications of CRISPR and how the ERA could work. In 2017 some R&D in crops could be advanced enough

Comment : Include with other NBT and SynBio topics

Page 3: [1] Comment **2015-12-17 6:41:00 PM**

We consider becasue of Examples of publications on the topic:

Monodehydroascorbate reductase mediates TNT toxicity in plants; Johnston, E. J., Rylott, E. L., Beynon, E., Lorenz, A., Chechik, V. & Bruce, N. C. 4 Sep 2015

Article in Science (New York, N.Y.)

Arabidopsis Glutathione Transferases U24 and U25 Exhibit a Range of Detoxification Activities with the Environmental Pollutant and Explosive, 2,4,6-Trinitrotoluene; Gunning, V., Tzafestas, K., Sparrow, H., Johnston, E. J., Brentnall, A. S., Potts, J. R., Rylott, E. L. & Bruce, N. C. 14 Apr 2014

Article in Plant Physiology

PRELIMINARY DOCUMENT DESIGNED TO INITIATE FURTHER DISCUSSION

14th INTERNATIONAL SYMPOSIUM ON THE BIOSAFETY OF GENETICALLY MODIFIED ORGANISMS (ISBGMO14)

(Guadalajara, Méexico, March 2017)

Monday, xx March MORNING			
	Welcome addresses -LOC -President of ISBR -Student Awards		
	Latin American delegate **Name**, *affiliation*		
	Plenary Session I: Advancing ERA of GM plants – The Past *Organizers:* **Name**, *affiliation* *(expression of interest: xxx)*		
Keynote	Overview of ERA questions posed when the first generation of GM plants reached the market **Phil McDonald**, *affiliation*		
	Experience gained on potential impacts of vertical gene flow *affiliation*		
	Experience gained on potential resistance evolution in target insect pests *affiliation*		
COFFEE BREAK			
	Experience gained on potential impacts on non-target organisms and the ecosystem services they contribute to (covering terrestrial, soil and aquatic organisms) *affiliation*		
	Experience gained on the assessment of potential unintended effects **Jaimie Schnell**, *affiliation*		
	Experience gained on potential impacts on food/feed safety *affiliation*		
	Panel discussion **Name**, *affiliation* (moderator)		
LUNCH			
AFTERNOON			
	Parallel Session I **Vertical gene flow between GM plants and sexually compatible relatives – dangerous liaisons or business as usual?** Organizers: ***Name, Affiliation***	**Parallel Session II** **Tiered approach fit for purpose to inform the NTO risk assessment of GM plants** Organizers: ***Name, Affiliation***	**Parallel Session III** **Types of evidence and efforts necessary to inform the safety assessment of unintended changes/traits in GM plants (Jaimie** Organizers: ***Name, Affiliation***
	xxx *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Gene Flow between GM corn and: conventional corn *Tripsacum*, and Teocintle. ~~Xxx~~ ~~**Name**, *affiliation*~~	Xxx **Name**, *affiliation*	Xxx **Name**, *Department of Animal Science, University of California, Davis* ~~*95616affiliation*~~
	~~Xxx~~ **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
COFFEE BREAK			
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx	Xxx	Xxx

Comment : Could you share with us what this figure of Latin American delegate means?

Comment : Is this suggestion to elaborate a sharp sentence of the basic question, the academic imperative or the productive/ regulatrory challenge?

Comment Consider if the time will be enouhg for the number of participants.

Comment : Could this talk touch also on persistance and invasivness?

Comment : Is this covering all kind of GMOs (mosquitoes, other insects, fish, bacteial inoculants)? →*see Parallel Session III*

Comment : This could include other corporate investigators of actual Bt events

Comment We propose in relation to ther paper: **Prevalence and impacts of genetically engineered feedstuffs on livestock populations, 2014.**

Comment

	Name, *affiliation*	**Name**, *affiliation*	**Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Poster Session I		
	Xxx		
	Xxx		
	Xxx		
	Xxx		

Tuesday, xx March MORNING			
Plenary Session II: Advancing ERA of GM plants – The Present *Organizers:* **Name**, *affiliation* *(expression of interest: xxx)*			
	Data harmonisation across jurisdictions **Name**, *affiliation*		
	Data relevance – problem formulation **Name**, *affiliation*		
	Data reliability – quality standards **Name**, *affiliation*		
	COFFEE BREAK		
	Data transportability **Name**, *affiliation*		
	Proportionality of data requirements **Name**, *affiliation*		
	Protection goals and environmental harm **Name**, *affiliation*		
	Panel discussion **Name**, *affiliation* (moderator)		
	LUNCH		
AFTERNOON			
	Parallel Session IV **Harmonisation and transportability of risk assessment data – criteria to assess the transportability of ERA data and ERAs performed in other jurisdictions** Organizers: ***Name, Affiliation***	**Parallel Session V** **ERA vs. ecological research – the relevance of a good problem formulation to ensure that gathered data are useful for ERA (organiser tbc)** Organizers: ***Name, Affiliation***	**Parallel Session VI** ~~xxx~~Contributions (actual and potential) of Biotech crops to to sustainable agriculture and adaptation to Climate Change Organizers: ***Name, Affiliation***
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation Productive Mexican scientists in this line, could participate*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx ~~**Name**~~, CGIAR Independent Science and Partnership Council Secretariat~~affiliation~~
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx ~~**Name**~~, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	COFFEE BREAK		
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	~~Xxx~~GE plants and Bioremediation Department of Biology (B/M219) University of York,United Kingdom ~~**Name**, *affiliation*~~
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Panel discussion	Panel discussion	Panel discussion

Comment : In the final context (all is risky), here the comparison or balance with benefits must be included (as a formal scheme or strategy)

Comment : This proposed session could correspond to the section on Protection goals. Also to review how GMO could contribuite to mitiagate effects of CC, in the big context since COP21 and MOP8-PCB 3 months before...

Comment : We expect some regulators interested in update normatives, may participate.

Comment

Comment Considering that she may have some actializations on the paper: Impact of GM crops on biodiversity (2011).

Comment We consider becasue of
Examples of publications on the topic:
Monodehydroascorbate reductase mediates TNT toxicity in plants; Johnston, E. J., Rylott, E. L., Beynon, E., Lorenz, A., Chechik, V. & Bruce, N. C. 4 Sep 2015
Article in Science (New York, N.Y.)
Arabidopsis Glutathione Transferases U24 and U25 Exhibit a Range of Detoxification Activities with the Environmental Pollutant and Explosive, 2,4,6-Trinitrotoluene; Gunning, V., Tzafestas, K., Sparrow, H., Johnston, E. J., Brentnall, A. S., Potts, J. R., Rylott, E. L. & Bruce, N. C. 14 Apr 2014
Article in Plant Physiology

	Name, *affiliation* (moderator)	**Name**, *affiliation* (moderator)	**Name**, *affiliation* (moderator)
	Poster Session II		
	Xxx		
	Xxx		
	Xxx		
	Xxx		
	Pecha Kucha Evening Session (dedicated to young researchers who are offered the opportunity to briefly present their on-going research activities)		
	Xxx		
	Xxx		
	Xxx		
	Xxx		

Wednesday, xx March MORNING			
	Parallel Session VII **Synthetic biology (organiser tbc)** Organizers: ***Name,*** *Affiliation*	**Parallel Session VIII** **Ecosystem services concept in the frame ERA of GMOs (and other stressors)** Organizers: ***Name,*** *Affiliation*	**Parallel Session IX** Latin American Session Organizers: ***Name,*** *Affiliation* **(Submitted presentations)**
	Xxx **Name**, *affiliation*	Protection goals, environmental harm and ecosystem services *affiliation*	~~Xxx~~Argentina´s experience on the regulated use of GM crops ~~**Name**~~ ~~*affiliation*~~*CONABIA?*
	Xxx **Name**, *affiliation*	Ecosystem services concept to make protection goals operational and define environmental harm **Name**, *EFSA representative*	~~Xxx~~The work of ICCA and the status of Central American countries on biosafety ~~**Name**~~ ~~*affiliation*~~*IICA*
	Xxx **Name**, *affiliation*	Ecosystem services as assessment endpoints *US EPA*	Xxx **Name**, ~~*affiliation*~~*Ecuador?*
	Xxx **Name**, *affiliation*	Interrelationship between ecosystem services and biodiversity **Name**, *affiliation*	Brazil´s experience on the regulated use of GM crops~~Xxx~~ ~~**Name**~~ (CIB-Brasil) or research leaders from ~~enoni~~, ~~*affiliation*~~*Embrapa*
	COFFEE BREAK		
	Xxx **Name**, *affiliation*	Trade-offs between protection goals **Name**, *affiliation*	Other LatAm countries (Uru, Par, Bol, Col)~~Xxx~~ ~~**Name**~~ (ArgenBio-ASA) or conctacs through her)~~ytes, *affiliation*~~
	Xxx **Name**, *affiliation*	Integrating the assessment of multiple stressors in ERA **Name**, *affiliation*	~~Xxx~~Researchers, entrpreneurship and Spin-off experiences ~~**Name**~~ Langebio-CINVESTAV,Stela Genomics ~~*affiliation*~~
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	~~Xxx~~ Biosafety research, regulatory development and judicial conflicts, Cibiogem **Name**, *affiliation*
	LUNCH		
AFTERNOON			
	SOCIAL PROGRAM **Field Trip and Dinner**		

Comment | : The Local committe would like to propose a Session on Latin American issues on biosafety, adoption, chalenges and opportunities

Thursday, xx March MORNING			
	Plenary Session III: Advancing ERA of GM plants – The Future *Organizers:* **Name**, *affiliation* *(expression of interest: xxx)*		
Keynote	ERA of GM plants – challenges ahead (sustainability of ecosystems, food security, climate change, innovation) *affiliation*		
	GM trees **Name** ~~*affiliation*~~*Oregon State University (Giancarlo Pasquali/ Embrapa -- Eucalyptus; Yuri Peña/ EcoSur-endangered tropical wooden species)*		
	GM grasses **Name**, *affiliation*		
	COFFEE BREAK		
	Output traits **Name**, *affiliation*		
	New plant biotechnology-based breeding techniques I – opportunities **Name**, *affiliation*		
	New plant biotechnology-based breeding techniques II – challenges (genome editing / gene drive technology) **Name**, *affiliation*		
	Panel discussion **Name**, *affiliation* (moderator)		
	LUNCH		
AFTERNOON			
	Parallel Session X **ERA considerations for RNAi-based GM plants – differences/similarities with GM plants expressing novel proteins** Organizers: ***Name, Affiliation***	**Parallel Session XI** **ERA considerations for GM insects** Organizers: ***Name, Affiliation***	**Parallel Session XII** ERA considerations for CRISPR- CAS-9 differences/ similarities with GM plants Organizers: ***Name, Affiliation*** **(Submitted presentations)**
	NTO testing under laboratory conditions *affiliation*	Overview of applications/technologies (development pipeline) *Intrexon/Oxitec*	~~Xxx~~New **Name**, *affiliation*
	NTO testing under laboratory and field conditions *affiliation*	Overview of ERA guidelines **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Transfer of dsRNA to higher trophic levels *affiliation*	ERA studies **Name**, *affiliation*	Xxx **Name**, *affiliation*
	COFFEE BREAK		
	eRNAi in arthropods or Fate of dsRNA in the soil *affiliation*	Gene drive overdrive **Name**, *affiliation* *NCSU-US*	Xxx **Name**, *affiliation*
	US EPA white paper **Name**, *affiliation*	UK Parliament & House of Lords inquiries **Name**, *affiliation*	Xxx **Name**, *affiliation*
	eRNAi in vertebrates *affiliation*	Weighing risks and benefits **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Panel discussion **Name**, *affiliation* (moderator)	Panel discussion **Name**, *affiliation* (moderator)	Panel discussion **Name**, *affiliation* (moderator)
	CLOSING SESSION		

Comment This is another proposal to start looking at the applications of CRISPR and how the ERA could work. In 2017 some R&D in crops could be advanced enough

s.19(1)

From:
To:
CC:
Date: 2016-01-05 8:35 AM
Subject: RE: ISBGMO14 - a tentative programme to trigger reactions
Attachments: DRAFT_Program_2015_11_19_sesionComments LOC V2 RJL_AFR.docx

Hi Everyone,
Thanks to all of you for sharing your thoughts, and especially to Yann for putting together the tentative program. I apologize for being essentially absent from these discussions for too long. I will try to take a more active role moving forward.

I have added my comments to the attached. I think there's a lot of good ideas in here, but my overarching concern is that a lot of this is well worn territory. Some of that is necessary because the same questions we were asking 20 years ago remain relevant to the biosafety field today, but I think we need to try to make sure that we are adding something new to the conference. This is why I find the synthetic biology session appealing. It will be challenging to pull off, but it will definitely bring a new and different perspective to the conference.

I really look forward to our next opportunity to discuss the program through a conference call.

Best,

PS I wholeheartedly support suggestion of a site visit. I've been in the office for an hour and I still can't feel my toes…

From:
Sent: Monday, January 4, 2016 12:12 PM
To:

Jaimie Schnell' <Jaimie.Schnell@inspection.gc.ca>
Cc:
Subject: RE: ISBGMO14 - a tentative programme to trigger reactions

and Group

Happy New Year – hope you all had a restful holiday break.

I like the latest round of comments and have added a few more on top of the version that sent out (see attached document).

Some general thoughts:

1. Looking backwards I think we have been planting enough crops in certain areas that we should be able to ask "so what happened?" – a few scenarios come to mind (a) Canada and canola – incredible market penetration… so what has happened environmentally? (b) USA maize and/or soy … what environmental effects have been seen? What about shifts in pesticide use? (c) Do we want to open a discussion on Monarchs in the USA – unintended consequences of weed control offered by glyphosate tolerant crops? (d) Are there stories for GM cotton in India and/or China in terms of environmental effects? (e) Do we want to bring up landscape level shifts due to adoption of GM crops – shifts is where you can grow certain crops economically due to weed control?

2. A few "hot" topics that keep coming up in the regulatory ERA world in the "present" include: ERA for stacks, ERA for LLP (low level presence in seed), ERA for Low Exposure Scenarios (low levels in

imported grain). Are there other "present" topics that should be discussed?

3. I wish we had a parallel session for submitted "short" papers – it would seem to involve more people in the meeting. Yes, the poster sessions are good, but short papers are good too.

4. In looking towards the future it seems that there is an amazing amount of work being done on lots of different crops and organisms. I suggest that we should find a way to bring in the folks doing work on bananas, apples, citrus, sorghum, rice, wheat, alfalfa, potato, jute, fish, etc. I wonder if any crops will not have GM versions within 10 years. So much of our ERA discussion seems to be maize centric, but some of the more challenging ERA's might in some of these "smaller" or "local" crops where not much previous ERA work has been done.

5. I like the increased attention being given to food/feed safety. I have long argued that food/feed safety is a topic that could be part of ISBGMO. Perhaps rather than a sporadic mention in a few talks it deserves a separate session on not just the "unintended effects" or "food/feed safety" but also a discussion on how food/feed risk assessment is conducted around the world (could include some thoughts on harmonization).

6. I suggest that we take all of the new breeding technology, CRISPR/CAS, and SynBio and put it into a single technical session. Then have a summary presentation in the final plenary session. That way the in-depth technical material is covered in one place for those interested in the details, and the "this is how ERA principles can be applied to new technologies" is in another place for the general audience for all to hear.

I think that the Synthetic Biology presentation would be (a) this is what SynBio is, (b) this is what types of "products" we might see in the future, and (c) this is how ERA principles can apply. One could expand the discussion to how it fits into the Cartegena Protocol process… While I believe that ISBGMO is the logical local to discuss "ERA and SynBio" I am not sure if the topic is far enough along to warrant an entire session.

Thanks.

From:
Sent: Monday, December 21, 2015 1:20 PM
To:

'Jaimie Schnell'

Cc:
Subject: RE: ISBGMO14 - a tentative programme to trigger reactions

Dear
Thank you for sharing the tentative programme.
We had the meeting of the Local Committee a few days ago and I am ready to share with you some initial reactions from the members, for your consideration and feedback.
We will keep working on some more issues (possible speakers, organizers, presentations tittles etc) but for now I hope this is useful.
Kind regards and best wishes

De:
Enviado el: jueves, 19 de noviembre de 2015 03:08 a. m.

s.19(1)

Para:

'Jaimie Schnell'

CC:
Asunto: ISBGMO14 - a tentative programme to trigger reactions

Dear ISBGMO14 scientific programme committee members,
Hi all,

It has been a while since you got bombarded by ISBGMO14-related eMails. Since an ISBR board conference call is scheduled in DEC somewhere, it is time to break the silence and translate the time of reflection into another set of valuable and concrete suggestions.

Building on the helpful thoughts exchanged so far and following a suggestion from I prepared the attached tentative scientific programme, consisting of:

- 3 plenary sessions (looking at the past, the present, and ahead)
- 12 parallel/break-out sessions (which zoom into a subset of the issues discussed at the plenary sessions)
- Pecha Kucha evening session
- Social event – afternoon with dinner

To ease our discussion, titles for sessions and talks are given, as well as potential session organisers and speakers. At this stage, most of the information is tentative/speculative, but it gives you a good indication of the progress made so far, and where we are heading to. I therefore would be very grateful if you could play the game, and share your thoughts on the draft proposal. Feel free to use track changes to revise the proposal.

I am fully aware it is too early to fix the programme and that flexibility should be ensured to allow the inclusion of "hot" issues that may arise in 2016. You will see that several slots are left open for this reason. Yet, our exercise may help us identify speakers we really would like to have on board, allowing us to approach them early in the process.

I must admit I am ignorant in the field of synthetic biology, so any feedback on this matter would be most welcomed.

Many thanks in advance,

Francais Deutsch Italiano Espanol Portugues Japanese Chinese Korean

http://www.DuPont.com/corp/email_disclaimer.html

s.19(1)

PRELIMINARY DOCUMENT DESIGNED TO INITIATE FURTHER DISCUSSION

14th INTERNATIONAL SYMPOSIUM ON THE BIOSAFETY OF GENETICALLY MODIFIED ORGANISMS (ISBGMO14)

(Guadalajara, México, March 2017)

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	Welcome addresses -LOC -President of ISBR -Student Awards		
	Latin American derJLlegatec **Name**, *affiliation*		
	Plenary Session I: Advancing ERA of GM plants – The Past *Organizers:* **Name**, *affiliation* *(expression of interest: xxxJEPA)*		
Keynotec	Overview of ERA questions posed when the first generation of GM plants reached the market **Phil McDonald**, *affiliation*		
	Experience gained on potential impacts of vertical gene flowSOG *affiliation*		
	Experience gained on potential resistance evolution RJLin target insect pests *affiliation*		
	COFFEE BREAK		
	Experience gained on potential impacts on non-target organisms and the ecosystem services they contribute to (covering terrestrial, soil and aquatic organisms) *affiliation*		
	Experience gained on the assessment of potential unintended RJLeffectsJEPA **Jaimie Schnell**, *affiliation*		
	Experience gained on on the assessment of food/feed safety *affiliation*		
	Panel discussion **Name**, *affiliation* (moderator)		
	LUNCH		
	AFTERNOON		
	Parallel Session I **Vertical gene flow between GM plants and sexually compatible relatives – dangerous liaisons or business as usual?** Organizers: ***Name, Affiliation***	**Parallel Session II** **Tiered approach fit for purpose to inform the NTO risk assessment of GM plants** Organizers: ***Name, Affiliation***JEPA	**Parallel Session III** **Types of evidence and efforts necessary to inform the safety assessment of unintended changes/traits in GM plants (Jaimie/** Organizers: ***Name, Affiliation***
	xxx *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Gene Flow between GM corn and: conventional corn *Tripsacum*, and Teocintle.	Xxx **Name**, *affiliation*	Xxx **Name** *Department of Animal Science, University of California, Davis 95616*
	NameRJL, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	COFFEE BREAK		
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx	Xxx	Xxx

	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Poster Session I		
	Xxx		
	Xxx		
	Xxx		
	Xxx		

s.19(1)

Tuesday, xx March MORNING			
Plenary Session II: Advancing ERA of GM plants – The PresentRJL *Organizers:* **Name**, *affiliation* *(expression of interest: xxx)*			
	Data harmonisation RJLacross jurisdictions **Name**, *affiliation*		
	Data relevance – problem formulation **Name**, *affiliation*		
	Data reliability – quality standards **Name**, *affiliation*		
	COFFEE BREAK		
	Data transportability **Name**, *affiliation*		
	Proportionality of data requirements **Name**, *affiliation*		
	Protection goals and environmental harmJEPA **Name**, *affiliation*		
	Panel discussion **Name**, *affiliation* (moderator)		
	LUNCH		
AFTERNOON			
	Parallel Session IV **Harmonisation and transportability of risk assessment data – criteria to assess the transportability of ERA data and ERAs performed in other jurisdictions** Organizers: ***Name,*** *Affiliation*JEPA	**Parallel Session V** **ERA vs. ecological research – the relevance of a good problem formulation to ensure that gathered data are useful for ERA (organiser tbc)** Organizers: ***Name,*** *Affiliation*	**Parallel Session VI** Contributions (actual and potential) of Biotech crops to to sustainable agriculture and adaptation to Climate Change Organizers: ***Name,*** *Affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation Productive Mexican scientists in this line, could participate*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx CGIAR Independent Science and Partnership Council Secretariat
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx *affiliation*SOG
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	COFFEE BREAK		
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	GE plants and Bioremediationsog. Professor of Biotechnology CNAP, Department of Biology (B/M219) University of York,United Kingdom
	Xxx	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*

	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Panel discussion **Name**, *affiliation* (moderator)	Panel discussion **Name**, *affiliation* (moderator)	Panel discussion **Name**, *affiliation* (moderator)
	Poster Session II		
	Xxx		
	Xxx		
	Xxx		
	Xxx		
	Pecha Kucha Evening Session (dedicated to young researchers who are offered the opportunity to briefly present their on-going research activities)		
	Xxx		
	Xxx		
	Xxx		
	Xxx		

s.19(1)

Wednesday, xx March MORNING			
	Parallel Session VII **Synthetic biology** **organiser tbc)** Organizers: ***Name,*** *Affiliation*	**Parallel Session VIII** **Ecosystem services concept in the frame ERA of GMOs (and other stressors)** Organizers: ***Name,*** *Affiliation*	**Parallel Session IX** **Latin American Session** Organizers: ***Name,*** *Affiliation* **(Submitted presentations)**
	Xxx **Name**, *affiliation*	Protection goals, environmental harm and ecosystem services *affiliation*	Argentina´s experience on the regulated use of GM crops *CONABIA?*
	Xxx **Name**, *affiliation*	Ecosystem services concept to make protection goals operational and define environmental harm **Name**, *EFSA representative*	The work of ICCA and the status of Central American countries on biosafety *IICA*
	Xxx **Name**, *affiliation*	Ecosystem services as assessment endpoints *US EPA*	Xxx **Name**, *Ecuador?*
	Xxx **Name**, *affiliation*	Interrelationship between ecosystem services and biodiversity **Name**, *affiliation*	Brazil´s experience on the regulated use of GM crops (CIB-Brasil) or research leaders from *Embrapa*
	COFFEE BREAK		
	Xxx **Name**, *affiliation*	Trade-offs between protection goals **Name**, *affiliation*	Other LatAm countries (Uru, Par, Bol, Col) (ArgenBio-ASA) or conctacs through her)
	Xxx **Name**, *affiliation*	Integrating the assessment of multiple stressors in ERA **Name**, *affiliation*	Researchers, entrpreneurship and Spin-off experiences Langebio-CINVESTAV,Stela Genomics
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Xxx **Name**, *affiliation*	Xxx **Name**, *affiliation*	Biosafety research, regulatory development and judicial conflicts, Cibiogem **Name**, *affiliation*
	LUNCH		
AFTERNOON			
	SOCIAL PROGRAM **Field Trip and Dinner**		

s.19(1)

Thursday, xx March MORNING			
	Plenary Session III: Advancing ERA of GM plants – The Future *Organizers:* **Name**, *affiliation* *(expression of interest: xxx)*		
Keynote	ERA of GM plants – challenges ahead (sustainability of ecosystems, food security, climate change, innovation) *affiliation*		
	GM trees *Oregon State University (Giancarlo Pasquali/ Embrapa --Eucalyptus; Yuri Peña/ EcoSur-endangered tropical wooden species)*		
	GM grasses **Name**, *affiliation*		
	COFFEE BREAK		
	Output traits **Name**, *affiliation*		
	New plant biotechnology-based breeding techniques I – opportunities **Name**, *affiliation*		
	New plant biotechnology-based breeding techniques II – challenges (genome editing / gene drive technology) **Name**, *affiliation*RJL		
	Panel discussion **Name**, *affiliation* (moderator)		
	LUNCH		
AFTERNOON			
	Parallel Session X **ERA considerations for RNAi-based GM plants – differences/similarities with GM plants expressing novel proteins** Organizers: ***Name,*** *Affiliation*AR	**Parallel Session XI** **ERA considerations for GM insects** Organizers: ***Name,*** *Affiliation*	**Parallel Session XII** **ERA considerations for CRISPR- CAS-9 differences/ similarities with GM plants** Organizers: ***Name,*** *Affiliation* **(Submitted presentations)**
	NTO testing under laboratory conditionsAR *affiliation*	Overview of applications/technologies (development pipeline) *Intrexon/Oxitec*	New **Name**, *affiliation*
	NTO testing under laboratory and field conditions *affiliation*	Overview of ERA guidelines **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Transfer of dsRNA to higher trophic levels AR *affiliation*	ERA studies **Name**, *affiliation*	Xxx **Name**, *affiliation*
	COFFEE BREAK		
	eRNAi in arthropods or Fate of dsRNA in the soilAR *affiliation*	Gene drive overdrive **Name**, *affiliation* *NCSU-US*	Xxx **Name**, *affiliation*
	US EPA white paper **Name**, *affiliation*	UK Parliament & House of Lords inquiries **Name**, *affiliation*	Xxx **Name**, *affiliation*
	eRNAi in vertebrates *affiliation*AR	Weighing risks and benefits **Name**, *affiliation*	Xxx **Name**, *affiliation*
	Panel discussion **Name**, *affiliation* (moderator)	Panel discussion **Name**, *affiliation* (moderator)	Panel discussion **Name**, *affiliation* (moderator)
	CLOSING SESSION		

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s.19(1)

From: Sarah G. Davis
To: Schnell, Jaimie
Date: 2016-01-08 12:12 PM
Subject: Fwd: RE: ISBGMO14 - a tentative programme to trigger reactions

Hey there,

I'm just catching up on emails

S.

>>> Jaimie Schnell 2015-12-21 4:04 PM >>>
No problem. The new job is going pretty well. It's interesting and busy work, which I like.

How are things back in PBRA and the rest of the directorate? I hope everyone is doing well and has a happy and healthy holiday!

Jaimie

>>> Sarah G. Davis 2015-12-21 3:48 PM >>>
Thanks very much Jaimie! How are things?

>>> Jaimie Schnell 2015-12-21 2:21 PM >>>

>>> 2015-12-21 2:20 PM >>>

Dear
Thank you for sharing the tentative programme.
We had the meeting of the Local Committee a few days ago and I am ready to share with you some initial reactions from the members, for your consideration and feedback.
We will keep working on some more issues (possible speakers, organizers, presentations tittles etc) but for now I hope this is useful.
Kind regards and best wishes

De:
Enviado el: jueves, 19 de noviembre de 2015 03:08 a. m.
Para:
Jaimie Schnell'
CC:
Asunto: ISBGMO14 - a tentative programme to trigger reactions

Dear ISBGMO14 scientific programme committee members,
Hi all,

It has been a while since you got bombarded by ISBGMO14-related eMails. Since an ISBR board

s.19(1)

conference call is scheduled in DEC somewhere, it is time to break the silence and translate the time of reflection into another set of valuable and concrete suggestions.

Building on the helpful thoughts exchanged so far and following a suggestion from I prepared the attached tentative scientific programme, consisting of:

- 3 plenary sessions (looking at the past, the present, and ahead)
- 12 parallel/break-out sessions (which zoom into a subset of the issues discussed at the plenary sessions)
- Pecha Kucha evening session
- Social event afternoon with dinner

To ease our discussion, titles for sessions and talks are given, as well as potential session organisers and speakers. At this stage, most of the information is tentative/speculative, but it gives you a good indication of the progress made so far, and where we are heading to. I therefore would be very grateful if you could play the game, and share your thoughts on the draft proposal. Feel free to use track changes to revise the proposal.

I am fully aware it is too early to fix the programme and that flexibility should be ensured to allow the inclusion of hot issues that may arise in 2016. You will see that several slots are left open for this reason. Yet, our exercise may help us identify speakers we really would like to have on board, allowing us to approach them early in the process.

I must admit I am ignorant in the field of synthetic biology, so any feedback on this matter would be most welcomed.

Many thanks in advance,

s.19(1)

From: Sarah G. Davis
To: Schnell, Jaimie
Date: 2016-01-19 4:02 PM
Subject: Fwd: Re: ISBGMO14 - a tentative programme to trigger reactions

Thanks Jaimie! Everything is going well over here. I hope your assignment is interesting and keeping you busy!

S.

>>> Jaimie Schnell 2016-01-19 2:47 PM >>>
Topic 1 looks super interesting....

I hope all is well over in PBRA!

Jaimie

>>> 2016-01-19 2:22 PM >>>
Hi All,
Sorry for the delay but two topics pertinent to this program have kept me underwater. I propose that the group consider including these topics into the program.
GE insects. Tomorrow I will be going to a meeting in California on gene drive technology in insects, sponsored by the Craig Venter Institute. The workshop involves who did the mosquito work, others involved in similar work and a whole bunch of regulators who are trying to figure out potential risks and how these organisms should be regulated. I think a session on gene drive is appropriate, novel and would make a great discussion. from the science standpoint and probably from EPA would be good choices for such a discussion. The other topic that has cornered my time is the use of GM insects with self-limiting genes, e.g., Oxtec technology. I see on the proposed program you have and from Oxitec which is fine. However, another active program in this area is the one with at North Carolina State (https://genetics.sciences.ncsu.edu/index.php/people/ and he could probably give a different slant since he doesn't have a company behind him. is doing work on GM screwworm (the original sterile insect project started in the 1950s using radiation) and also the spotted wing Drosophila. I think having a program that includes insect control by **self-limiting genes and gene drive**, and the regulations around them would be very attractive to the overall program.
Regulating GM food crops in developing countries. As you know, Bangladesh commercialized Bt eggplant in late 2013 and in 2015 100+ farmers grew it. The only reason it was approved in Bangladesh was the political will of the Prime Minister, which trumped the situation in India where there is still a moratorium. I believe that a discussion on regulatory challenges in developing countries like Bangladesh (and a host of others to come) would be very worthwhile. knows about this first-hand.

My 2 cents.

Cornell University/NYSAES, Barton Lab 416
630 W. North St., Geneva, NY 14456
Ph FAX 315 787-2326; Cell
http:/ .entomology.cornell.edu/
http://ip.cals.cornell.edu

From:
Date: Tuesday, January 5, 2016 8:34 AM

To:

'Jaimie Schnell' <Jaimie.Schnell@inspection.gc.ca>
Cc:
Subject: RE: ISBGMO14 - a tentative programme to trigger reactions

Hi Everyone,
Thanks to all of you for sharing your thoughts, and especially to for putting together the tentative program. I apologize for being essentially absent from these discussions for too long. I will try to take a more active role moving forward.

I have added my comments to the attached. I think there's a lot of good ideas in here, but my overarching concern is that a lot of this is well worn territory. Some of that is necessary because the same questions we were asking 20 years ago remain relevant to the biosafety field today, but I think we need to try to make sure that we are adding something new to the conference. This is why I find the synthetic biology session appealing. It will be challenging to pull off, but it will definitely bring a new and different perspective to the conference.

I really look forward to our next opportunity to discuss the program through a conference call.

Best,

From:
Sent: Monday, January 4, 2016 12:12 PM
To:

s.19(1)

'Jaimie Schnell' <Jaimie.Schnell@inspection.gc.ca>
Cc:
Subject: RE: ISBGMO14 - a tentative programme to trigger reactions

and Group

Happy New Year - hope you all had a restful holiday break.

I like the latest round of comments and have added a few more on top of the version that sent out (see attached document).

Some general thoughts:

<!--[if !supportLists]-->1. <!--[endif]-->Looking backwards I think we have been planting enough crops in certain areas that we should be able to ask "so what happened?" - a few scenarios come to mind (a) Canada and canola - incredible market penetration… so what has happened environmentally? (b) USA maize and/or soy … what environmental effects have been seen? What about shifts in pesticide use? (c) Do we want to open a discussion on Monarchs in the USA - unintended consequences of weed control offered by glyphosate tolerant crops? (d) Are there stories for GM cotton in India and/or China in terms of environmental effects? (e) Do we want to bring up landscape level shifts due to adoption of GM crops - shifts is where you can grow certain crops economically due to weed control?
<!--[if !supportLists]-->2. <!--[endif]-->A few "hot" topics that keep coming up in the regulatory ERA world in the "present" include: ERA for stacks, ERA for LLP (low level presence in seed), ERA for Low Exposure Scenarios (low levels in imported grain). Are there other "present" topics that should be discussed?
<!--[if !supportLists]-->3. <!--[endif]-->I wish we had a parallel session for submitted "short" papers - it would seem to involve more people in the meeting. Yes, the poster sessions are good, but short papers are good too.

s.19(1)

<!--[if !supportLists]-->4. <!--[endif]-->In looking towards the future it seems that there is an amazing amount of work being done on lots of different crops and organisms. I suggest that we should find a way to bring in the folks doing work on bananas, apples, citrus, sorghum, rice, wheat, alfalfa, potato, jute, fish, etc. I wonder if any crops will not have GM versions within 10 years. So much of our ERA discussion seems to be maize centric, but some of the more challenging ERA's might in some of these "smaller" or "local" crops where not much previous ERA work has been done.
<!--[if !supportLists]-->5. <!--[endif]-->I like the increased attention being given to food/feed safety. I have long argued that food/feed safety is a topic that could be part of ISBGMO. Perhaps rather than a sporadic mention in a few talks it deserves a separate session on not just the "unintended effects" or "food/feed safety" but also a discussion on how food/feed risk assessment is conducted around the world (could include some thoughts on harmonization).
<!--[if !supportLists]-->6. <!--[endif]-->I suggest that we take all of the new breeding technology, CRISPR/CAS, and SynBio and put it into a single technical session. Then have a summary presentation in the final plenary session. That way the in-depth technical material is covered in one place for those interested in the details, and the "this is how ERA principles can be applied to new technologies" is in another place for the general audience for all to hear.

I think that the Synthetic Biology presentation would be (a) this is what SynBio is, (b) this is what types of "products" we might see in the future, and (c) this is how ERA principles can apply. One could expand the discussion to how it fits into the Cartegena Protocol process... While I believe that ISBGMO is the logical local to discuss "ERA and SynBio" I am not sure if the topic is far enough along to warrant an entire session.

Thanks.

s.19(1)

From:
Sent: Monday, December 21, 2015 1:20 PM
To:
'Jaimie Schnell'
Cc:
Subject: RE: ISBGMO14 - a tentative programme to trigger reactions

Dear
Thank you for sharing the tentative programme.
We had the meeting of the Local Committee a few days ago and I am ready to share with you some initial reactions from the members, for your consideration and feedback.
We will keep working on some more issues (possible speakers, organizers, presentations tittles etc) but for now I hope this is useful.
Kind regards and best wishes

De:
Enviado el: iueves. 19 de noviembre de 2015 03:08 a. m.
Para:
'Jaimie Schnell'
CC: '
Asunto: ISBGMO14 - a tentative programme to trigger reactions

Dear ISBGMO14 scientific programme committee members,
Hi all,

It has been a while since you got bombarded by ISBGMO14-related eMails. Since an ISBR board conference call is scheduled in DEC somewhere, it is time to break the silence and translate the time of reflection into another set of valuable and concrete suggestions.

Building on the helpful thoughts exchanged so far and following a suggestion from I prepared the attached tentative scientific

s.19(1)

programme, consisting of:

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<!--[if !supportLists]-->· <!--[endif]-->12 parallel/break-out sessions (which zoom into a subset of the issues discussed at the plenary sessions)
<!--[if !supportLists]-->· <!--[endif]-->Pecha Kucha evening session
<!--[if !supportLists]-->· <!--[endif]-->Social event - afternoon with dinner

To ease our discussion, titles for sessions and talks are given, as well as potential session organisers and speakers. At this stage, most of the information is tentative/speculative, but it gives you a good indication of the progress made so far, and where we are heading to. I therefore would be very grateful if you could play the game, and share your thoughts on the draft proposal. Feel free to use track changes to revise the proposal.

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I must admit I am ignorant in the field of synthetic biology, so any feedback on this matter would be most welcomed.

Many thanks in advance,

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s.19(1)

From: Jaimie Schnell
To: Davis, Sarah G.
Date: 2016-01-21 10:53 AM
Subject: Fwd: AW: ISBGMO14 - a tentative programme to trigger reactions

>>> 2016-01-21 10:39 AM >>>

and colleagues,

I finally found some time to look through all the comments provided on the draft program.

First of all I like what I see. There is lots of interesting things out there.

I'm more interested to look into the future. Thus we should make sure that the session I that deals with the past really focuses on "what have we learned for the future". Having said this I wonder whether we should/could cut back Parallel Session I and II to simply 1 or 2 talks on the subject. This would provide space for other topics that have been suggested.

I like in particular the proposed sessions on
- the contribution of GMOs to climate change (but we need to make sure that this is related to questions of biosafety)
- Latin America
- Food/feed safety (currently numerous EU-funded projects are running that address for example the value of rat studies) (see mail by from January 4)
- Regulatory challenges in developing countries (see mail by from January 19)

But I also like to stress the fact that we should provide space for submitted (short) talks (see mail by from January 4). We have learned from past ISBGMOs that this makes the meeting more attractive to many people. In many cases people are only allowed to participate if they have a slot to present. So I propose that we first decide whether we reserve two or three parallel session for submitted talks and then discuss the content of the remaining parallel sessions.

Regards,

Von:
Gesendet: Donnerstag, 19. November 2015 10:08
An: I

'Jaimie Schnell'
<Jaimie.Schnell@inspection.gc.ca>
Cc: '
Betreff: ISBGMO14 - a tentative programme to trigger reactions

Dear ISBGMO14 scientific programme committee members,
Hi all,

s.19(1)

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I must admit I am ignorant in the field of synthetic biology, so any feedback on this matter would be most welcomed.

Many thanks in advance,

s.16(2)(c)

s.21(1)(b)

From: Jaimie Schnell
To: Davis, Sarah G.; Girard, Cecile; Levac, Dylan
Date: 2016-02-12 3:35 PM
Subject: Re: AHTEG/ Roadmap
Attachments: CFIA_ACIA_-_#7773944_-_vR_-_PBRA-AHTEG_on_RA&RM.DRF

Hi guys,

I did a quick search of my documents for anything I had on the AHTEG and put together the attached folder. Sadly there are only 2 documents. One is an intervention in an online discussion, and the other is comments on the Roadmap. I can squeeze in a quick chat before 5 today if you're interested, but I'm not around on Monday. I'm at 773-7491 if you do want to give me a call today.

Cheers,
Jaimie

>>> Sarah G. Davis 2016-02-12 2:06 PM >>>
Hi all,

I note that the current comment period for the online forum on RA/RM closes February 15 (i.e. this Monday). Is it possible to bump up this meeting, in case we decide it's worthwhile to contribute Canadian comments? Just a thought.

Sarah

>>> Cecile Girard 2016-02-05 9:21 AM >>>
to gain insight into Jaimie's work and participation in the online expert discussions on the Roadmap and the modules under it, Thanks Jaimie!
I booked room 3E-104 at Camelot however this is the conference call information just in case .
Call-in number : (613) 960 7516
Conference ID:

Dear and members of the open-ended group and AHTEG,

Please allow me to respond to the changes proposed by
provided many valuable modifications. In particular, on line 67, I agree that it is important to consider that many effects may in fact be neutral. Also, on lines 554-560, the suggested changes to the text on monitoring help to clarify this section. I also agree that the phrasing of the paragraph at lines 554-558 could lead to endless cycles of risk assessment and management decisions. Risk management is typically only considered in cases where the risk is considered to be unacceptable. If the text in this paragraph is kept, it should be made clear that an unacceptable level of risk is the starting point for considering risk management options.

In regards to the text which was added that relates to addressing global climatic and environmental changes (lines 58-59, 71-72, 467-468), although it is recognized that such changes are occurring, and these should be considered where possible as part of the risk assessment, in practice this is difficult to do primarily because it is difficult to predict exactly what those changes will be. As a result, these considerations often do not play a predominant role in the risk assessments. In practice, lines 90-92 are considered to be more effective for addressing such concerns, because they allow for a re-assessment of the LMO whenever such changes are recognized to have occurred.

Also, in regards to the text added on lines 240-241 ("Preferably, comparators should be organisms with long history of safe use"), the use of a comparator with a long history of safe use, although it may be preferable, it may not always be practical, nor is it entirely necessary. I am concerned that the inclusion of this statement may create a barrier for LMOs that are being introduced as a new crop in the country conducting the risk assessment. In such situations, experimental data from field studies can be used to develop a case for the safety of the LMO without a need to rely on the history of safe use of the comparator. Restricting the development of LMOs such that only species with a long history of safe use are used is outside the scope of this document.

Thank you for the opportunity to comment.

Regards,
Jaimie

Convention on Biological Diversity

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GUIDANCE ON RISK ASSESSMENT OF LIVING MODIFIED ORGANISMS

This document was developed by the Ad Hoc Technical Expert Group (AHTEG) on Risk Assessment and Risk Management under the Cartagena Protocol on Biosafety.[1]

This is intended to be a **"**living document**"** that will be improved with time as new experience becomes available and new developments in the field of applications of living modified organisms (LMOs) occur, as and when mandated by the Parties to the Cartagena Protocol on Biosafety.

PART I:

ROADMAP FOR RISK ASSESSMENT OF LIVING MODIFIED ORGANISMS

This "Roadmap" provides an overview of the process of environmental risk assessment for a living modified organism (LMO) in accordance with Annex III[2] to the Cartagena Protocol on Biosafety (hereinafter "the Protocol") and all other articles related to risk assessment. This Roadmap was developed in response to decision BS-IV/11[3] of the Conference of the Parties serving as the meeting of the Parties to the Protocol (COP-MOP). Annex III is the basis of the Roadmap. Accordingly, this Roadmap is a guidance document and does not replace Annex III. The overall aim of the Roadmap is facilitating and enhancing the effective use of Annex III by elaborating the technical and scientific process of how to apply the steps and points to consider in the process of risk assessment.

The purpose of this Roadmap is to provide further guidance on using Annex III with additional background material and links to useful references relevant to risk assessment. The Roadmap may be useful as a reference for risk assessors when conducting or reviewing risk assessments and in capacity-building activities.

The Roadmap applies to all types of LMOs[4] and their intended uses within the scope and objective of the Protocol, and in accordance with Annex III. However, it has been developed based largely on living modified crop plants because of the extensive experience to date with environmental risk assessments for these organisms. It is intended to be a "living document" that will be modified and improved on over time

---

[1] The AHTEG on Risk Assessment and Risk Management was established by the Conference of the Parties serving as the meeting of the Parties to the Cartagena Protocol on Biosafety (COP-MOP) in its decision BS-IV/11. The terms of reference for the AHTEG as set out by the Parties may be found in the annex to decision BS-IV/11 (http://bch.cbd.int/protocol/decisions/decision.shtml?decisionID=11690).

[2] http://www.cbd.int/biosafety/articles.shtml?a=cpb-43 .

[3] http://www.cbd.int/biosafety/cop-mop/results/?id=11690 .

[4] Including products thereof, as described in paragraph 5 of Annex III to the Protocol.

UNEP

Secretariat of the Convention on Biological Diversity
United Nations Environment Programme
413 Saint-Jacques Street, Suite 800, Montreal, QC, H2Y 1N9, Canada
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secretariat@cbd.int www.cbd.int

as and when mandated by COP-MOP, and in the light of new experience, information and developments in the field of applications of LMOs, e.g. when other types of LMOs have been evaluated more extensively in environmental risk assessments.

INTRODUCTION

General introduction

Background

In accordance with the precautionary approach[5] the objective of the Protocol is "to contribute to ensuring an adequate level of protection in the field of the safe transfer, handling and use of LMOs resulting from modern biotechnology that may have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health, specifically focusing on transboundary movements".[6]

For this purpose, Parties shall ensure that risk assessments are carried out when making informed decisions regarding LMOs.

The novel combination of genetic material in ~~A~~an LMO ~~and its use~~ may have several effects, which may be intended or unintended and these effects may vary depending on how the LMO is used.~~, taking into account that some unintended effects may be predictable.~~ The objective of risk assessment is to *identify* and *evaluate* the potential adverse effects of LMOs on the conservation and sustainable use of biological diversity in the likely potential receiving environment, taking also into account risks to human health.[7] The risk assessment is performed on a case-by-case basis. What is considered an adverse effect depends on protection goals and assessment end-points taken into consideration when scoping the risk assessment. The choice of protection goals by the Party could be informed by Articles 7(a), 7(b) and 8(g) and Annex 1 of the Convention on Biological Diversity. It should also be taken into consideration that adverse effects are not limited to those that result from the novel combinations of genetic materials in LMOs. The interaction of any plant with the environment can also result in adverse effects, as can many agronomic practices. The adverse effects that result from the novel combination of genetic material in an LMO should be considered in the broader context of these adverse effects.

Comment [s1]: The relevance of being able to predict unintended effects is not clear. It should be deleted or elaborated.

Comment [s2]: It would be useful to include a glossary defining such terms as case-by-case, protection goals and assessment end-points.

Comment [s3]: It would be useful to include a discussion on how to define adverse effects based on protection goals and assessment end-points.

According to Article 15 of the Protocol, risk assessments shall be based, at a minimum, on information provided in accordance with Article 8 and other available scientific evidence in order to identify and evaluate the possible adverse effects of LMOs on the conservation and sustainable use of biological diversity, taking also into account risks to human health.[8]

Annex III of the Protocol states that "risk assessment should be carried out in a scientifically sound and transparent manner, and can take into account expert advice of, and guidelines developed by, relevant international organizations. Lack of scientific knowledge or scientific consensus should not necessarily be interpreted as indicating a particular level of risk, an absence of risk, or an acceptable risk. (…) Risk assessment should be carried out on a case-by-case basis. The required information may vary in nature

[5] "In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation" (Principle 15 of the Rio Declaration on Environment and Development) at: (http://www.unep.org/Documents.Multilingual/Default.asp?DocumentID=78&ArticleID=1163), and in line with Articles 10.6 and 11.8 of the Protocol.

[6] http://www.cbd.int/biosafety/articles.shtml?a=cpb-01 .

[7] Annex III, paragraph 1.

[8] Article 15, paragraph 1.

and level of detail from case to case, depending on the LMO concerned, its intended use and the likely potential receiving environment".[9]

The risk assessment process

Risk assessment is a structured process. Paragraph 8 of Annex III provides a description of the key steps of the risk assessment process to identify and evaluate the potential adverse effects and identify strategies to manage risks. Paragraph 9 describes, depending on the case, points to consider in this process. The steps describe an integrated process whereby the results of one step may be relevant to other steps. Also, risk assessment may need to be conducted in an iterative manner, where certain steps may be repeated or re-examined to increase or re-evaluate the confidence in the conclusions of the risk assessment. When new information arises that could change its conclusions, the risk assessment may need to be re-examined accordingly. Similarly, the issues mentioned in the 'overarching issues' section below can be taken into consideration again at the end of the risk assessment process to determine whether the objectives and criteria that were set out at the beginning of the risk assessment have been met.

Risk assessment is done in a comparative manner, meaning that risks associated with the novel genotypic and phenotypic characteristics of the living modified organisms should be considered in the context of the risks posed by the ~~non-modified~~ recipient organism in the likely potential receiving environment.[10] Additionally, experience with the same, or, as appropriate, similar, genotypic or phenotypic characteristics in other organisms may be taken into consideration along with the ~~non-modified~~ recipient organism in the risk assessment of an LMO. The other organisms may be of the same or different species as the LMO and can extend to other LMOs. ~~For instance, the comparison with the (near-)isogenic or closely related non-modified recipient is used in step 1 of the risk assessment (see below) where the novel genotypic or phenotypic characteristics associated with the LMO are identified. But when the potential consequences of adverse effects are evaluated, broader experience, such as mentioned in step 3 (a), may be taken into account, when establishing a baseline.~~ Results from experimental field trials or other environmental information and experience with the same LMO may be taken into account as information elements in a new risk assessment for that LMO. In all cases where information, including baseline data, is derived from other sources, it is important to establish the validity and relevance of the information for the risk assessment. For instance, it should be taken into account that the behavior of a transgene,[11] as that of any other gene, may vary because it depends on the genetic and physiological background of the recipient as well as on the ecological characteristics of the environment that the LMO is introduced into.

The concluding recommendations derived from the risk assessment in step 5 are required to be taken into account in the decision-making process on an LMO. In the decision-making process, other Articles of the Protocol or other relevant issues may also be taken into account, but these are outside of the scope of this Roadmap ~~and are addressed in the last paragraph of this Roadmap: 'Related Issues'~~.

A flowchart illustrating the risk assessment process according to this Roadmap is annexed hereto.

›› See references relevant to "General Introduction":
http://bch.cbd.int/onlineconferences/roadmapref_ahteg_ra.shtml#introduction

Comment [s4]: It would be more useful if each of these points were not simply reiterated, but further explained. In some cases, these concepts are also introduced elsewhere in the document, creating. For instance, scientific soundness is addressed in the Overarching Issues section, The concept of case-by-case is first introduced two paragraphs above.

Comment [s5]: An example would be useful to explain this point.

Comment [s6]: Comparisons outside of the non-modified recipient organism are useful throughout the risk assessment process. Step 1 is not merely an identification of the novel characteristics alone, but an identification of those that may have adverse effects. This stage would therefore certainly benefit from knowledge of the genotypic or phenotypic characteristics in other LMOs and other species. It is for this reason that the text below was deleted.

Overarching issues in the risk assessment process

There are some overarching issues to consider in the design/planning phase of the risk assessment process to ensure the quality and relevance of the information used. These entail, among others:

[9] Annex III, paragraphs 3, 4 and 6.

[10] Annex III, paragraph 5.

[11] For the purpose of this document, a transgene is a nucleic acid sequence in an LMO that results from the application of modern biotechnology as described in Article 3 (i) (a) of the Protocol.

- Setting criteria for relevancy in the context of a risk assessment. Only information that contributes to the identification and evaluation of the potential adverse effects of the LMO on the conservation and sustainable use of biological diversity in the likely potential receiving environment, taking also into account risks to human health, should be considered. ~~e.g. data may be considered relevant if they can affect the outcome of the risk assessment.~~

- Establishment of scientifically robust criteria for the inclusion of scientific ~~information~~data.
    - Data should be of an acceptable scientific quality. Data quality should be consistent with the accepted practices of scientific evidence-gathering and reporting and may include independent review of the methods and designs of studies. Data may be derived from a variety of sources, e.g. new experimental data as well as data from relevant peer reviewed scientific literature.
    - Sound science is based on ~~transparency,~~ verifiability, and reproducibility (e.g. reporting of methods and data in sufficient detail, so that the resulting data and information could be confirmed independently), and on the accessibility of data (e.g. the availability of relevant, required data or information or, if requested and as appropriate, of sample material), taking into account the provisions of Article 21 of the Protocol on the confidentiality of information. The provisions of sound science serve to ensure and verify that the risk assessment is carried out in a scientifically sound ~~and transparent~~ manner.

- Identification and consideration of uncertainty.

  According to the Protocol, "where there is uncertainty regarding the level of risk, it may be addressed by requesting further information on the specific issues of concern or by implementing appropriate risk management strategies and/or monitoring the living modified organism in the receiving environment".[12] It should be kept in mind that uncertainty cannot always be reduced by providing additional information. For example, new uncertainties may arise as a result of the provision of additional information.

  Uncertainty is inherent in the concept of risk. To date, "there is no internationally agreed definition of 'scientific uncertainty', nor are there internationally agreed general rules or guidelines to determine its occurrence. Those matters are thus dealt with – sometimes differently – in each international instrument incorporating precautionary measures".[13, 14]

  ~~It should be kept in mind that uncertainty cannot always be reduced by providing additional information. For example, new uncertainties may arise as a result of the provision of additional information.~~

  Considerations of uncertainty strengthen the confidence and scientific soundness of a risk assessment. In communicating the results of a risk assessment, it is important to consider and analyze in a systematic way the various forms of uncertainty that can arise at each step and in combination at step 4 of the Roadmap. An analysis of uncertainty includes considerations of its source and nature.

Comment [s7]: This point was not clearly articulated. The suggested text is intended to ameliorate this. It would be useful to further illustrate this point with an example of information that would not be useful. For instance, information relating to the adverse effects following gene introgression into wild species for a species that does not outcross.

Comment [s8]: It is not clear from this section how to address uncertainty. Also, the idea that uncertainty is inherent in risk should be expanded further. Otherwise, risk assessors may enter into an endless loop of requesting more information to reduce uncertainty, when uncertainty can in fact never be eliminated. Better guidance on when additional information should be sought should be provided.

[12] Annex III, paragraph 8 (f).

[13] *An Explanatory Guide to the Cartagena Protocol on Biosafety*, paragraph 57 (http://data.iucn.org/dbtw-wpd/edocs/EPLP-046.pdf).

[14] Article 10, paragraph 6, of the Protocol: "Lack of scientific certainty due to insufficient relevant scientific information and knowledge regarding the extent of the potential adverse effects of a living modified organism on the conservation and sustainable use of biological diversity in the Party of import, taking also into account risks to human health, shall not prevent that Party from taking a decision, as appropriate, with regard to the import of the living modified organism in question (…), in order to avoid or minimize such potential adverse effects."

The *source(s)* of uncertainty may stem from the data/information itself and/or the choice of study design including the methods used, and the analysis of the information.

The *nature* of uncertainty may be described for each identified source of uncertainty arising from: (i) imperfect knowledge or lack of available information, which may be reduced with more research/information, and (ii) inherent variability.

›› See references relevant to "Identification and consideration of uncertainty":
http://bch.cbd.int/onlineconferences/roadmapref_ahteg_ra.shtml#uncertainty

Context and scoping of the risk assessment

In setting the context and scope for a risk assessment, a number of aspects should be taken into consideration, as appropriate, that are specific to the Party involved and to the specific case of risk assessment. These aspects include:

- Existing policies and strategies based on, for instance,: (i) rRegulations and the international obligations of the Party involved; (ii) Guidelines or regulatory frameworks that the Party has adopted; and (iii) Protection goals, assessment end-points, risk thresholds and management strategies. Setting the context and scope for a risk assessment that are consistent with these policies, strategies and protection goals may involve a process that includes risk assessors, decision-makers and various stakeholders prior to conducting the actual risk assessment;
- (i) Framing the risk assessment process, by: (ii) Taking into account the expected (potential) conditions of handling and use of the LMO; and (iii) Taking into account customary practices and habits that could affect the protection goals or end-points; identification of relevant questions to be asked for that purpose;
- Identification of methodological and analytical requirements, including any reviewing mechanisms, that is required to achieve the objective of the risk assessment as laid down, for instance, in guidelines published or adopted by the Party that is responsible for conducting the risk assessment (i.e. typically the Party of import according to the Protocol);
- The nature and level of detail of the information required may depend on the intended use of the LMO and the likely potential receiving environment. This applies, in particular, to different release scenarios. For instance, For small scale field releases, especially at early experimental stages, less information may be available compared to the information available for large scale environmental release, and for commercial scale plantingtypically for small scale field releases, there is limited information on the characteristics of the LMO. In order to manage potential risks that cannot be qualified due to this limited information, conditions are applied to instead minimize exposure of the LMO to the environment and thereby reduce the likelihood of any adverse effects occurring. These risk management approaches should be considered in the risk assessment;
- Experience and history of use of the non-modified recipient, taking into account its ecological function;[15] and
- Establishing criteria for describing the level of the (potential) environmental adverse effects of LMOs, as well as criteria for the terms that are used to describe the levels of likelihood (step 2), the magnitude of consequences (step 3) and risks (step 4) and the manageability of risks (step 5; see risk assessment steps below).

Comment [s9]: Unclear what these may be. An example would helpful.

›› See references relevant to "Context and scoping of the risk assessment":
http://bch.cbd.int/onlineconferences/roadmapref_ahteg_ra.shtml#context

[15] The term "ecological function" (or: "ecological services") provided by an organism refers to the role of the organism in ecological processes. Which ecological functions or services are taken into account here will be dependent on the protection goals set for the risk assessment. For example, organisms may be part of the decomposer network playing an important role in nutrient cycling in soils or be important as a pollen source for pollinators and pollen feeders.

THE RISK ASSESSMENT

To fulfill its objective under Annex III, as well as other relevant Articles of the Protocol, risk assessment is performed in five steps, as appropriate. These five steps are indicated in Paragraph 8 (a)-(e) of Annex III and also detailed below. Their titles have been taken directly from the paragraphs 8 (a)-(e) of Annex III.

For each step a rationale and points to consider are provided. Some points to consider are taken from paragraph 9 of Annex III, whereas others have been added based on generally accepted methodology of LMO risk assessment and risk management. The relevance of each point to consider will depend on the case being analyzed.

›› See references relevant to "Risk Assessment in general":
http://bch.cbd.int/onlineconferences/roadmapref_ahteg_ra.shtml#riskassessment

Step 1: "An identification of any novel genotypic and phenotypic characteristics associated with the living modified organism that may have adverse effects on biological diversity in the likely potential receiving environment, taking also into account risks to human health." [16]

Rationale:

The purpose of this step is to identify ~~biological changes~~novel genotypic or phenotypic characteristics resulting from the genetic modification(s)~~, including any deletions,~~ compared to the ~~non-modified~~recipient organism, and identify what, if any, ~~changes~~ characteristics could cause adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health. This step is similar to the 'hazard identification step' in other risk assessment guidance. In order to identify the novel genotypic or phenotypic characteristics, ~~The comparison of~~ the LMO is ~~performed with~~compared to the ~~non-modified~~ recipient organism, or a (near-)isogenic line or, as appropriate, with an ~~non-modified~~ organism of the same species. Both the intended~~, taking into consideration the~~ new ~~trait(s)~~characteristic(s) of the LMO should be confirmed and any potential unintended traits that may have adverse effects should be identified. Experience with the novel genotypic or phenotypic characteristics in other organisms, including other LMOs and other species, may be used to identify potential adverse effects that could be caused by those characteristics. Those novel characteristics that are determined to cause no adverse effects are not considered further in the risk assessment. If no adverse effects are identified, the risk assessment is complete.

In this step, scientifically plausible scenarios are identified in which the novel characteristics of the LMO could give rise to adverse effects in an interaction with the likely potential receiving environment. ~~The novel characteristics of the LMO to be considered can be genotypic or phenotypic, biological. They may be intended or unintended, predicted or unpredicted.~~ The points to consider below provide information elements on which hazard identification can be built.

~~The type and level of detail of the information required in this step may vary from case to case depending on the nature of the modification of the LMO and on the scale of the intended use of the LMO. For small scale field releases, especially at early experimental stages, less information may be available and some of the resulting uncertainty may typically be addressed by risk management measures (see step 5~~).

Points to consider regarding the characterization of the LMO:

Comment [s10]: This text was deleted because it places undo emphasis on deletions.

Comment [s11]: More guidance should be provided to describe how to determine which phenotypic characteristics to examine. This is also done through hazard identification based on protection goals and assessment end-points. Without this guidance, an exhaustive comparison of any and every phenotypic characteristics may be undertaken, much of which would be irrelevant for the risk assessment.

Comment [s12]: This text is already included in the context and scoping section and does not need to be reiterated here.

[16] The bold printed headings of each step are direct quotes from Annex III of the Protocol.

(a) Relevant characteristics of the ~~non-modified~~ recipient organisms (e.g. (i) its biological characteristics, in particular those that, if changed~~, or interacting with the new gene products or traits of the LMO,~~ could cause changes in the behavior of the ~~non-modified~~ recipient in the environment in a way that may cause adverse effects; (ii) its taxonomic relationships, (iii) its origin, centers of origin and centers of genetic diversity); (iv) ecological function, and (v) ~~as a component of~~its contribution to biological diversity that is important for the conservation and sustainable use of the biological diversity in the context of Article 7(a) and Annex I of the Convention. This information can be used to develop a baseline to which the LMO can be compared in order to identify novel characteristics. In other cases, this information may be used to identify whether the novel characteristics may cause adverse effects. For instance, if the recipient organism, as an ecological function, acts as a source of pollen to pollinators and pollen feeders, then changes that relate to pollen characteristics should be considered for the adverse effect they may have on this function;

Comment [s13]: This text was unclear. Any such interactions would presumably have to result in a change in the biological characteristics in order for it to cause an adverse effect and this is therefore captured in the remaining text.

~~(b) Relevant characteristics of the genes and of other functional sequences, such as promoters, that have been inserted into the LMO (e.g. functions of the gene and its gene product in the donor organism with particular attention to characteristics that could cause adverse effects in the recipient);~~

Comment [s14]: Recommend that this text be deleted since it is redundant with the subsequent point.

(c) ~~Molecular~~ Novel genotypic characteristics of the LMO related to the modification ~~(e.g. (a) characteristics of the insert(s) which may include (i) gene products (intended and unintended), (ii) levels of expression, (iii) functions, (iv) insertion site in the genome of the recipient and any effects of insertion, (v) stability or integrity within the genome of the recipient; (b) (i) the transformation method, (ii) the characteristics of the vector if and, as far as it is present in the LMO, including its identity, source or origin and host range)~~ with particular attention paid to any characteristics that are related to potential adverse effects. The availability and relevance of this information may vary according to the type of application. This information can help to identify novel characteristics of the LMO (e.g., a gene has been inserted and that gene produces a novel protein) as well as determine whether the novel characteristic could potentially cause an adverse effect (e.g., the source of the gene is an organism with no known toxicity or allergencity and so the novel protein is unlikely to be toxic or allergenic). ~~Characteristics related to adverse effects may also result from changed expression levels of endogenous genes due to effects of a transgene or from combinatorial effects;~~[17]

Comment [s15]: Recommend that this text be deleted because the level of detail was not in keeping with the level of detail found in the other points to consider.

Comment [s16]: Adverse effects related to changed expression levels of endogenous genes or from combinatorial effects are more likely to be captured as part of the phenotypic analysis of the LMO. Their inclusion here could suggest that attempts be made to identify such effects at the molecular level, which would be difficult and inefficient.

(d) ~~Consideration of~~Novel ~~genotypic (see point to consider (c) above) and~~ phenotypic~~, biological changes~~characteristics in the LMO, either intended or unintended, in comparison with the ~~non-modified~~ recipient~~, considering those changes that could cause adverse effects~~. Changes identified in comparison to the recipient can also be considered in the context ~~These may include changes at the transcriptional and translational level and may be due to the insert itself or to genomic changes due to the transformation or recombination processes.~~of the range of that characteristic within reference plant lines, which typically include a range of genotypes representative of the natural variation in the crop species and may include other LMOs. Changes identified in comparison with the recipient are not considered to be biologically relevant if they are within the range observed in the reference plant lines.

[17] For the purpose of this document, the term "combinatorial effects" refers to effects that may arise from the interactions between two (or more) genes. The effects may occur at the level of gene expression, or through interactions between RNA, or among gene products. The effects may be qualitative or quantitative; quantitative effects are often referred to as resulting in antagonistic, additive or synergistic effects.

Point to consider regarding the receiving environment:

(e) Characteristics of the likely potential receiving environment, in particular its attributes that are relevant to potential interactions of the LMO that could lead to adverse effects (see also paragraph (g) below),[18] taking into account the characteristics that are components of biological diversity. For instance, adverse effects that would occur after gene flow to wild relatives do not need to be considered if there are no wild relatives present in the receiving environment;

(f) The intended scale and duration of the environmental release.

Points to consider regarding the potential adverse effects resulting from the interaction between the LMO and the receiving environment:

(g) Characteristics of the LMO ~~in~~that relat~~ione~~ to its interaction with the receiving environment (e.g. information on phenotypic traits that are relevant for its survival in, or its potential adverse effects on the likely receiving environment – see also paragraph (e) above);

(h) ~~Considerations for~~Influence of unmanaged and managed ecosystems (such as agricultural, forest and aquaculture systems) ~~that are relevant~~in ~~for~~ the likely potential receiving environment on the interaction of the LMO with the receiving environment. For instance, ~~These include~~ the potential for dispersal of the LMO through~~, for instance,~~ seed dispersal or outcrossing within or between species, or through transfer into habitats where the LMO may persist or proliferate may depend on the management status of the ecosystem;

(i) Potential ~~consequences of~~for outcrossing and gene flow ~~of transgenes~~ from an LMO to other sexually compatible species, which could lead to introgression of the transgene(s) into the population of sexually compatible species and the potential for this to result in an adverse effect;

(j) Effects on ~~non-target~~other living organisms in the receiving environment;

(k) ~~Cumulative effects;~~[19]

(l) Effects of the incidental exposure of humans to (parts of) the LMO (e.g. exposure to pollen), and the toxic or allergenic effects that may ensue; and

(m) Potential adverse effects as a consequence of horizontal gene transfer (HGT) of transgenic sequences from the LMO to any other organism in the likely receiving environment. ~~With regard to HGT to~~HGT will only be a consideration for some species. For instance, HGT is more common for micro-organisms (including viruses), whereas for plants it is a rare occurrence and therefore does not need to be considered in the risk assessment~~, particular attention may be given to cases where the LMO is also a micro-organism; and~~.

~~(n) A consideration of uncertainty arising in step 1 that may significantly impact the identification of hazards in this step (see "Identification and consideration of uncertainty" under "Overarching issues in the risk assessment process" above).~~

Comment [s17]: Other LMOs in the environment should be considered as another aspect of the receiving environment. They deserve no more consideration than the diversity of other organisms with which an LMO would interact in the receiving environment. It places undo emphasis on other LMOs. Recommend that this point be deleted.

Comment [s18]: Supporting reference: Keese 2008. Environ. Biosafety Res. 7: 123–149.

Comment [s19]: Given that uncertainty is addressed in the overarching issues section, it does not need to be reiterated in each of the steps. Recommend that this text be deleted

[18] Examples of relevant attributes of the receiving environment include, among others: (i) ecosystem type (e.g., agroecosystem, horticultural or forest ecosystems, soil or aquatic ecosystems, urban or rural environments); (ii) extension of dimension (small, medium, large or mixed scale); (iii) previous use/history (intensive or extensive use for agronomic purposes, natural ecosystem, or no prior managed use in the ecosystem); (iv) the geographical zone(s) in which the release is intended, including climatic and geographic conditions and the properties of soil, water and/or sediment; (v) specific characteristics of the prevailing faunal, floral and microbial communities including information on sexually compatible wild or cultivated species; and (vi) biodiversity status, including the status as centre of origin and diversity of the recipient organism and the occurrence of rare, endangered, protected species and/or species of cultural value.

[19] For the purpose of this document, the term "cumulative effects" refers to effects that occur due to the presence of multiple LMOs in the receiving environment.

›› See references relevant to "Step 1":
http://bch.cbd.int/onlineconferences/roadmapref_ahteg_ra.shtml#step1

Step 2: "An evaluation of the likelihood of adverse effects being realized, taking into account the level and kind of exposure of the likely potential receiving environment to the living modified organism."

Rationale:

The potential adverse effects identified in step 1 may ~~result in~~pose a risk~~s~~, but this depends on the likelihood and the consequence of the effects. An adverse effect must have some likelihood of occurring and the consequences must have some magnitude in order for it to pose a risk. If either the likelihood is determined to be negligible or the consequences are determined to be marginal, then the risk of that adverse effect is correspondingly considered to be negligible. The likelihood of adverse effects being realized is considered in this step and the consequences should the adverse effects be realized are considered in Step 3. ~~In order to determine and characterize the overall risk (in step 4), the likelihood of each adverse effect being realized has to be assessed and evaluated beforehand.~~

One aspect to be considered is whether the receiving environment will be exposed to the LMO in such a way that the identified adverse effects may actually occur, e.g. taking into consideration the intended use of the LMO, and the expression level, dose and environmental fate of transgene products as well as plausible pathways leading to adverse effects. For instance, if a novel protein is determined to be toxic to a non-target organism, but it is not expressed in tissues to which that non-target organism is exposed, adverse effects are unlikely to be realized. The plausible scenarios elucidated in Step 1 should include several conditions that must be met in order for the adverse effect to be realized. At this stage in the risk assessment, the degree to which each of those conditions will be met should be considered in order to rate the likelihood.

Comment [s20]: An example of a plausible scenario and the conditions that should be considered would be useful here.

~~Other aspects to be considered here are (i) the potential of the LMO (or its derivatives resulting from outcrossing) to spread and establish beyond the receiving environment (in particular into protected areas), and whether that could result in adverse effects; and (ii) the possibility of occurrence of adverse (e.g. toxic) effects on organisms (or on organisms other than the 'target organism' for some types of LMOs).~~

Comment [s21]: These aspects should be considered during the hazard identification stage (Step 1). Recommend that this text be deleted.

The levels of likelihood may be expressed, for example, by the terms 'highly likely', 'likely', 'unlikely', 'highly unlikely'. Parties may consider describing these terms and their uses in risk assessment guidelines published and/or adopted by them.

Points to consider:

(a) Information relating to the type and intended use of the LMO, including the scale and duration of the release, bearing in mind, as appropriate, user habits, patterns and agronomic practices. For instance, a common practice for small scale releases is to impose conditions that limit the exposure of the environment to the LMO so as to minimize the likelihood of any adverse effects occurring. Such considerations should be taken into account during the risk assessment;

(b) The relevant characteristics of the likely potential receiving environment that may experience or may be a factor in the occurrence of the potential adverse effects (see also step 1 (e), (f) and (g)), taking into account the variability of the environmental conditions and any long-term adverse effects. Levels of expression in the LMO and persistence and accumulation in the environment (e.g. in the food chain) of substances with potentially adverse effects newly produced by the LMO, such as insecticidal proteins, toxins and allergens;

(c) Available information on the location of the release and the receiving environment (such as geographic and biogeographic information, including, as appropriate, coordinates, information on the sexually compatible species and whether they are co-localized with the LMO and whether flowering occurs at the same time, or in general, interbreeding can occur);

(d) For ~~the~~ cases ~~of~~ where outcrossing and outbreeding from an LMO to sexually compatible species is possible and a potential adverse effect may occur following introgression of the transgene into the sexually compatible species, the considerations as to whether outcrossing and outbreeding is likely to occur would include: (i) the biology of the sexually compatible species; (ii) the potential environment where the sexually compatible species may be located; (iii) the chance of introgression of the transgene into the sexually compatible species;

~~(e)~~ Expected exposure to the environment where the LMO is released and means by which incidental exposure could occur at that location or elsewhere (e.g. gene flow or incidental exposure due to losses during transport and handling);

~~(f)(e) A consideration of uncertainty arising in step 2 (see "Identification and consideration of uncertainty" under "Overarching issues in the risk assessment process" above).~~

›› See references relevant to "Step 2":
http://bch.cbd.int/onlineconferences/roadmapref_ahteg_ra.shtml#step2

Step 3: "An evaluation of the consequences should these adverse effects be realized."

Rationale:

This step describes an evaluation of the magnitude of the consequences in the likely potential receiving environment, taking into account, among others, results of tests done under different conditions such as laboratory experiments or experimental field releases. The evaluation is comparative and should be considered in the context of the adverse effects caused by the ~~non-modified~~ recipient or, if more appropriate, by a near-isogenic or other ~~non-modified~~ organism of the same species. Comparison to other LMOs or other species that express a similar novel characteristic may also be informative for determining potential consequences. The evaluation may also be considered in the context of the adverse effects that occur in the environment and which are associated with existing practices such as various agronomic practices, for example, for pest or weed management if such information is available and relevant. The evaluation of the consequence of adverse effects may be expressed as, for instance, 'major', 'intermediate', 'minor' or 'marginal'. Parties may consider describing these terms and their uses in risk assessment guidelines published and/or adopted by them.

Points to consider:

~~(a) Relevant experience with the consequences of existing practices with the non-modified recipient or, if more appropriate, with an non-modified organism of the same species in the likely potential receiving environment, may be useful in order to establish baselines to evaluate, for example, the consequences of (i) agricultural practices, such as the level of inter- and intra-species gene flow, dissemination of the recipient, abundance of volunteer plants in crop rotation; occurrence of pests and/or beneficial organisms such as pollinators and pest predators; or (ii) pest management, including effects on non-target organisms in pesticide applications while following accepted agronomic practices;~~

~~(b) Adverse effects which may be direct and indirect, immediate and delayed. Some of these adverse effects may result from combinatorial and cumulative effects;~~

Comment [s22]: The relevance of this information for the consequences of an adverse effect are unclear. Recommend that the text be deleted.

Comment [s23]: Adverse effects should be identified in Step 1. This point to consider is therefore out of place. Recommend that this text be deleted.

(c) Results from laboratory experiments examining, *inter alia*, dose-response relationships (e.g., EC 50s, LD 50s) and from field trials evaluating, for instance, potential invasiveness;

~~(d) For the case of outcrossing to sexually compatible species, the possible adverse effects that may occur, after introgression, due to the expression of the transgenes in the sexually compatible species; and~~

~~(e)A consideration of uncertainty arising in step 3 that may significantly impact the evaluation of consequences should the adverse effects be realized (see "Identification and consideration of uncertainty" under "Overarching issues in the risk assessment process" above).~~

Comment [s24]: Again, this relates to hazard identification, not a consideration of the consequences of an adverse effect. Recommend that this text be deleted.

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›› See references relevant to "Step 3":
http://bch.cbd.int/onlineconferences/roadmapref_ahteg_ra.shtml#step3

Step 4: "An estimation of the overall risk posed by the living modified organism based on the evaluation of the likelihood and consequences of the identified adverse effects being realized."

Rationale:

The purpose of this step is to determine and characterize the level of the overall risk based on the ~~identified individual risks~~likelihood and consequences of the adverse effects posed by the LMO on the conservation and sustainable use of biological diversity, taking also into account human health. The ~~individual risks are determined on the~~is step takes into consideration the ~~basis of an~~ analysis of the potential adverse effects identified in step 1, their likelihood (step 2) and consequences (step 3), and also tak~~inges~~ into consideration any relevant uncertainty that emerged in the preceding steps.

It should then be determined whether the assessed risks meet the criteria set out in the protection goals, assessment endpoints and thresholds, as established in relevant legislation of the Party or in its practice. ~~Where there is uncertainty regarding the level of risk~~In cases where uncertainties preclude a conclusion about the overall risk, it may be necessary to addressed the uncertainty by requesting further information on the specific issues of concern or by implementing appropriate risk management strategies and/or monitoring the LMO in the receiving environment (see also step 5). Description of the risk characterization may be expressed as, for instance, 'high', 'medium', 'low', 'negligible' or 'indeterminate due to uncertainty or lack of knowledge'. Parties may consider describing these terms and their uses in risk assessment guidelines published and/or adopted by them.

Comment [s25]: How this should be done is not clear.

To date, there is no universally accepted method to estimate the overall risk but rather a number of methods are available for this purpose. The outcome of this step may be, for example, a conclusion as to the overall risk along with a description explaining how the estimation of the overall risk was performed.

Comment [s26]: It would be useful to include a description of a couple of the preferred methods here.

Points to consider:

(a) The identified potential adverse effects (step 1);

(b) The assessments of likelihood (step 2);

(c) The evaluation of the consequences (step 3);

~~(d) Any interaction between the identified individual risks;~~

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~~(e) Any cumulative effect due to the presence of multiple LMOs in the receiving environment; and~~

Comment [s27]: Both of these points should be considered during steps 1 to 3.

(f) A consideration of uncertainty arising in this and the previous steps (see "Identification and consideration of uncertainty" under "Overarching issues in the risk assessment process" above).

›› See references relevant to "Step 4":
http://bch.cbd.int/onlineconferences/roadmapref_ahteg_ra.shtml#step4

Step 5: "A recommendation as to whether or not the risks are acceptable or manageable, including, where necessary, identification of strategies to manage these risks"

Rationale:

In this way, step 5 provides an interface between the process of risk assessment and the process of determining whether risk management measures are necessary and, if so, which measures could be implemented to manage the risks associated with the LMO.

If ~~T~~the evaluation of the overall risk ~~on the basis of the identified individual risks~~ conducted in the previous step ~~may~~ leads to the conclusion that the ~~identified risks are~~overall risk is not acceptable in relation to the established protection goals, assessment end-points and risk thresholds~~, also when taking into account risks posed by the non-modified recipient and its use.~~, ~~T~~then the question arises whether risk management options can be identified that have the potential to ~~remove~~ reduce the identified risks ~~or reduce their magnitude~~. In the process of the formulation of risk management options, the effect of the proposed options on the identified risks should be explained. The appropriate steps of the risk assessment should then be reiterated by taking into account the implementation of the risk management options to estimate the new levels of likelihood, consequence and risk and to assess if the risk management measures are appropriate and sufficient.

The issues mentioned in the 'overarching issues' section can be taken into consideration again at the end of the risk assessment process to evaluate whether the objectives and criteria that were set out at the beginning of the risk assessment have been met.

The recommendation of acceptability of risk(s) should acknowledge the previously identified uncertainties. Some uncertainties may be reduced by monitoring (e.g. checking the validity of assumptions about the ecological effects of the LMO), requests for more information, or implementing the appropriate risk management options.

The recommendation(s) as to whether or not the risks are acceptable or manageable and recommendations for risk management options are submitted for consideration in the decision-making process.

Points to consider related to the acceptability of risks:

~~(a)~~ The criteria for the establishment of acceptable/unacceptable levels of risk, including those set out in national legislation or guidelines, as well as the protection goals of the Party, as identified when setting the context and scope for a risk assessment; ~~In establishing a baseline for the comparison of the LMO, any relevant experience with the use of the non-modified recipient, and practices associated with its use in the potential receiving environment; and~~

(b) ~~The feasibility of the adoption of risk management or monitoring strategies.~~

Comment [s28]: These points are not relevant for this step. The feasibility of risk management or monitoring strategies is not a consideration during risk assessment but during decision-making.

Points to consider related to the risk management strategies:

(c) Existing management practices, if applicable, that are in use for the ~~non-modified~~ recipient organism or for other organisms that require comparable risk management and that might be appropriate for the LMO being assessed, e.g. isolation distances to reduce outcrossing potential of the LMO, modifications in herbicide or pesticide management, crop rotation, soil tillage, etc.;

(d) Methods to detect and identify the LMO and their specificity, sensitivity and reliability in the context of environmental monitoring (e.g. monitoring for short- and long-term, immediate and

delayed effects; specific monitoring on the basis of scientific hypotheses and supposed cause/effect relationship as well as general monitoring) including plans for appropriate contingency measures to be applied in case the results from monitoring call for them;

(e) ~~Management options in the context of the intended use (e.g. mitigating the effect of an LMO producing insecticidal proteins by the use of refuge areas to minimize the development of resistance against these proteins).~~

Comment [s29]: This is not relevant to risk assessment. Recommend that this text be deleted.

›› See references relevant to "Step 5":
http://bch.cbd.int/onlineconferences/roadmapref_ahteg_ra.shtml#step5

~~RELATED ISSUES~~

~~Some members of the AHTEG considered some issues to be related to risk assessment and decision-making process but outside the scope of this Roadmap. These issues were, *inter alia*:~~

- ~~Risk management (Article 16);~~
- ~~Capacity-building (Article 22);~~
- ~~Public awareness and participation (Article 23);~~
- ~~Socio-economic considerations (Article 26);~~
- ~~Liability and redress (Article 27);~~
- ~~Co-existence;~~
- ~~Ethical issues.~~

Comment [s30]: Such a list of issues is likely to confuse more so than be helpful. A general caveat that there are other factors to be considered in decision-making outside of the risk assessment is appropriate in the introduction, but a full list such as this is not useful, as well as being outside the scope of this document.

Annex

FLOWCHART FOR RISK ASSESSMENT

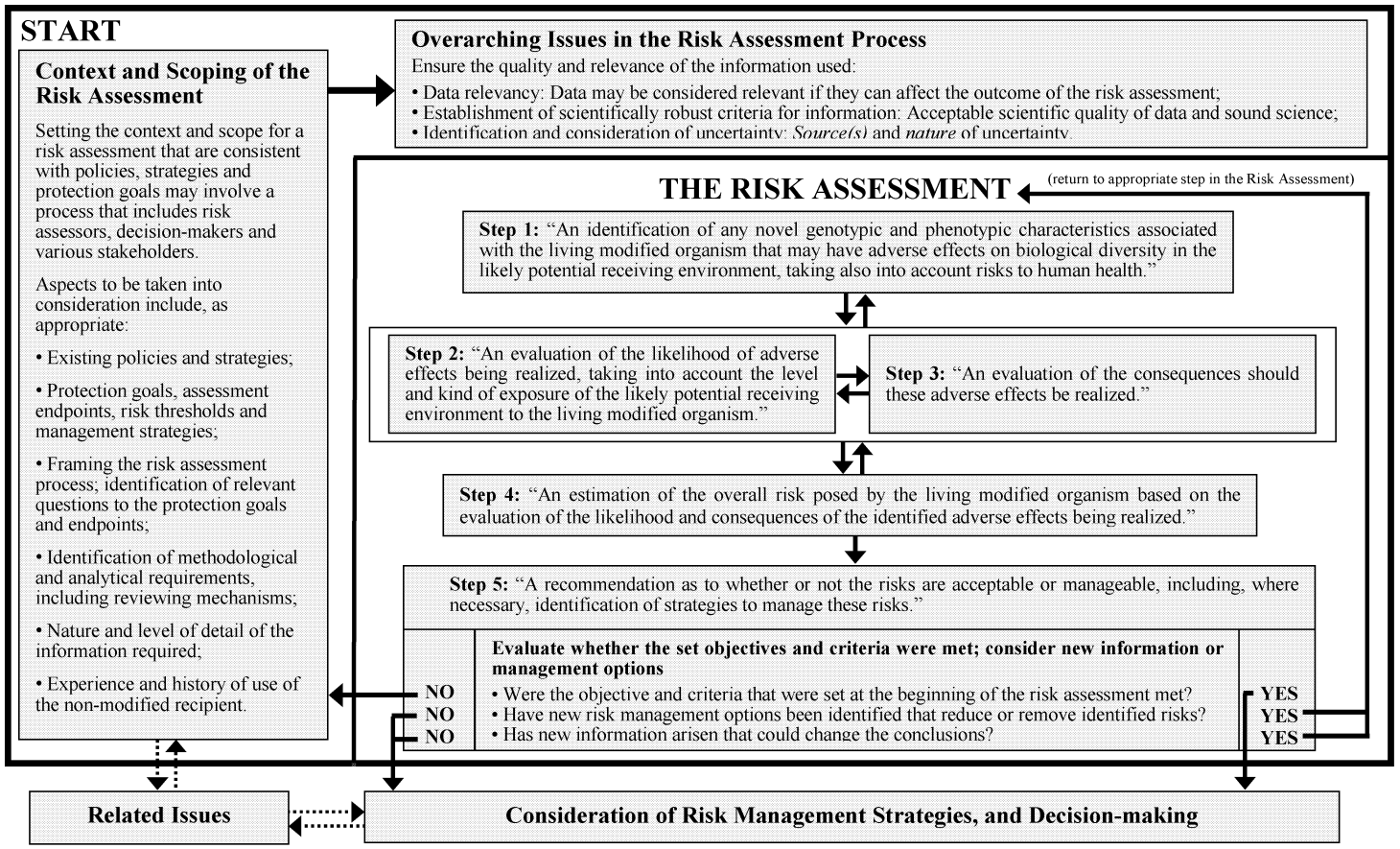

Figure 1. The Roadmap for Risk Assessment. The flowchart represents the steps to *identify* and *evaluate* the potential adverse effects of LMOs on the conservation and sustainable use of biological diversity in the likely potential receiving environment, taking also into account risks to human health. The box around steps 2 and 3 shows that these steps may sometimes be considered simultaneously or in reverse order.

Comment [s31]: The points in the box under Step 5 have been wrongly lumped into this step. They should exist as separate considerations. A conclusion describing these final checks should be added.

If no potential adverse effects are identified in Step 1, the risk assessment does not need to proceed any further. This is not captured in the flow diagram.

PART II

SPECIFIC TYPES OF LMOs AND TRAITS

A. RISK ASSESSMENT OF LIVING MODIFIED ORGANISMS WITH STACKED GENES OR TRAITS

INTRODUCTION

Worldwide, a growing number of LMOs with stacked transgenic traits, particularly LM crops, are being developed for commercial uses. As a result, the number of stacked genes in a single LMO and the number of LMOs with two or more transgenic traits is growing.

Stacked transgenic traits can be produced through different approaches. In addition to the cross-~~hybridising~~ breeding of two LMOs, multiple trait characters can be achieved by transformation with a multigene cassette, retransformation of an LMO or simultaneous transformation with different transgene cassettes (i.e., cotransformation).

This guidance document focuses on stacked transgenic traits that have been produced through cross-breeding of two or more LMOs.

LMOs with multiple transgenic traits resulting from re-transformation, co-transformation or transformation with a multigene cassette should be assessed according to the Roadmap.

This guidance document complements the Roadmap for Risk Assessment developed by the AHTEG on Risk Assessment and Risk Management, and focuses on issues that are of particular relevance to the risk assessment of LMOs with stacked events generated through cross breeding of single or multiple event LMO, should the decision be made to do a risk assessment on an LMO with stacked events.

This is intended to be a "living document" that will be shaped and improved with time as new information and/or experience becomes available and new developments in the field of applications of LMOs occur, as and when mandated by the Parties to the Protocol.

OBJECTIVE

The objective of this document is to give additional guidance on the risk assessment (RA) of LMOs with stacked events generated through conventional crossing of single or multiple event LMOs. Accordingly, it is meant to complement the Roadmap for Risk Assessment[20] and address special aspects of LMOs with stacked transgenes/traits resulting from the conventional crossing. For the time being it will be restricted to plant LMOs.[21]

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[20] In accordance with a mandate from the Parties to the Cartagena Protocol on Biosafety (the Protocol), the AHTEG has developed 'a "roadmap", such as a flowchart, on the necessary steps to conduct a risk assessment in accordance with Annex III to the Protocol and, for each of these steps,' has provided 'examples of relevant guidance documents'. The Roadmap is presented, together with the present document, to the Parties of the Protocol on the occasion of the fifth meeeting of the Conference of the Parties serving as the meeting of the Parties.

[21] It is also restricted to those LMO generated through the methods of Modern Biotechnology as defined in Art. 3 (i) (a) of the Protocol. LMOs derived from fusion of cells are not covered in this document.

USE OF TERMS

Transformation event (TraEv)

For the purpose of this document, a transformation event (TraEv) is an LM plant which results from the use of modern biotechnology applying *in vitro* nucleic acid techniques[22] that may involve, but is not limited to, single or multiple gene transformation cassettes. In either case, the result will be one transformation event.

Stacked event (StaEv)

For the purpose of this document, a stacked event (StaEv) is an LM plant generated through conventional cross breeding of two or more single parental transformation events (TraEvs) or two already stacked events. Accordingly the transgene[23] cassettes may be physically unlinked (i.e. located separately in the genome) and may segregate independently.

Unintentional stacked event

Unintentional stacked events are the result of outcrossing of stacked events into other LMOs or compatible relatives in the receiving environment. Depending on the segregation pattern of the stacked genes this may result in new and/or different combinations of TraEvs.

SCOPE

This guidance document focuses on stacked events (StaEv) resulting from conventional crossings between two or more single transformation events (TraEv) as parental lines so that the resulting LMO contains two or more transgenic traits. It is understood that the individual TraEvs making up the StaEv have been assessed previously in accordance with Annex III of the Cartagena Protocol on Biosafety and as described in the Roadmap.

ISSUES TO BE CONSIDERED IN THE RISK ASSESSMENT

Assessment of sequence characteristics at the insertion sites and genotypic stability *(see step 1, Point to consider (c) of the Roadmap for Risk Assessment)*

Rationale:

~~Although recombination, mutation and rearrangements are not limited to LMOs, the combination of transgenic traits via cross~~During breeding, ~~may further~~ changes may occur to the molecular characteristics of the inserted genes/gene fragments at the insertion site ~~and/or influence the regulation of the expression of the transgenes~~ as a result of endogenous plant processes, such as recombination and mutation, that act on the genome. Such changes will equally occur to transgenes and endogenous plant sequences. Transgenes with similar genetic sequences may be more likely to undergo recombination, since homologous recombination acts on genomic regions that have identical or highly similar sequence. Alternatively, complex inserts with multiple repeats are known to be less stable and could also be more likely to undergo rearrangements during breeding. The latter should be known as part of the risk assessment for the original TraEvs and in most cases only stable inserts will be selected for development.

Comment [s32]: In my opinion, the information obtained from repeating the molecular characterization on an LMO with stacked events is unlikely to be of great value. Any changes that may occur are unlikely to be related to the presence of two stacked events and are equally likely to occur during any stage of breeding as well as being equally likely to occur to any sequence in the genome, not just transgenes. My recommendation is to remove this section from the guidance document. If this section remains, I recommend the following modifications to provide some context.

Comment [s33]: Changes in transgene expression are addressed in the next section so this text was deleted

Comment [s34]: Supporting references: Mumm and Walters 2001. Crop Science 41: 1381–1389; Gaut et al. 2007. Nature Reviews Genetics 8: 77–84 ; Choffnes et al. 2001. In Vitro Cell. Dev. Biol.–Plant 37: 756–762; Puchta and Hohn 1996. Trends in Plant Science Reviews 1: 340–348.

[22] See Article 3 (i) (a) of the Protocol.

[23] For the purpose of this document, a transgene is a nucleic acid sequence that results from the application of modern biotechnology as described in Article 3 (i) (a) of the Protocol.

In addition, changes to the molecular characteristics may influence the ability to detect the LMO, which may be needed in the context of risk management measures (see step 5 of the Roadmap). The ~~reappraisal of the molecular sequence at the insertion sites, and the intactness of the transgenes may be confirmative to the~~ molecular characteristics of the ~~parental LMOs~~StaEv can be examined~~, but may also be a basis for assessing any intended or unintended possibly adverse effects on the conservation and sustainable use of biological diversity in the likely potential receiving environment and of potential adverse effects on human health~~ if it is thought likely that a change may have occurred. If different molecular characteristics are observed, the potential for them to result in adverse effects should be considered following the steps of the Roadmap. Alternatively, a phenotypic characterization can also be used to identify any unintended changes to the StaEv compared to the TraEvs that may have resulted from such molecular changes. Any detection and identification methods for the TraEvs can be tested on the StaEv to determine if they are still suitable. If they are no longer deemed to be suitable, new tests specific for the StaEv can be developed, as necessary. The extent of the reexamination may vary case by case and should take into account the results of the parental LMO risk assessment.

Assessment of potential interactions between combined events and the resulting phenotypic effects
(see step 1, point to consider (d) of the Roadmap for Risk Assessment)

Rationale:

It is possible that ~~T~~the combination of two or more TraEvs resulting in a StaEv may influence the expression level of each of the transgenes. Differences in gene expression in StaEv may be attributable to variation in the genetic background, which can influence transgene expression. This is not unique to StaEvs, as it can occur with any breeding. Changes in gene expression that may be specifically attributable to a StaEv are most likely to occur if the transgenes from the two TraEvs bear similar genetic elements, and at least one of the transgenes produces aberrant RNA triggering gene silencing. If differences in expression are observed, it should be considered whether the differences would change any of the conclusions from the original risk assessments performed for each of the TraEvs.

Comment [s35]: Supporting references: Graham et al. 2011. *In* C.N. Stewart, Jr. et al. (eds.) Plant Transformation Technologies p. 171–196; Kohli et al. 1999. Planta 208: 88–97.

~~and there may be interaction between the genes and the expressed products of the different transgenes.~~ In addition, the stacked transgenes may alter the expression of endogenous genes. As above, this is most likely to occur if transgenes from the TraEvs bear genetic elements that are similar to an endogenous sequence, and at least one of the transgenes produces an aberrant RNA triggering gene silencing. This is best assessed at the phenotypic level by determining if the StaEv has any phenotypic characteristics that are novel in comparison to the TraEvs.

There may also be interactions between the expressed products of the two transgenes that alter one or more of the novel phenotypic characteristics observed in the TraEvs or that result in a phenotypic characteristic that is novel in the StaEv as compared to the TraEvs. This is most likely to occur if the gene products ~~Therefore, in addition to information about the characteristics of the parental single-TraEv LMOs, specific information on potential for interactions between the altered or inserted genes, stacked proteins or modified traits and endogenous genes and their products in the StaEv LMO should be considered and assessed. For example, it should be assessed whether the different transgenes~~ affect the same biochemical pathways or physiological processes~~, or are expected to or may have any combinatorial effects that may result in potential for new or increased adverse effects relative to the parent LMOs.~~ Consideration can be given as to whether interactions between the expressed products are likely and whether that interaction may have an adverse effect. This may also be assessed by characterizing the phenotype of the StaEv and determining if it possesses any phenotypic characteristics that are novel in comparison to the TraEvs. This should be done according to the steps outlined in the Roadmap.

~~**Assessment of combinatorial and cumulative effects of stacked event LMOs on the conservation and sustainable use of biological diversity in the likely potential receiving environment, taking also**~~

into account potential adverse effects to human health *(see step 1, point to consider (c), step 2, point to consider (c) and step 3, point to consider (b) of the Roadmap for Risk Assessment)*

Rationale:

Assessment of combinatorial and cumulative effects[24] is based on the environmental risk assessment data for the StaEv LMO in comparison to the closely related non-modified recipient species and the parent LMOs in the likely receiving environment, taking into consideration the results of the genotypic and phenotypic assessments outlined above.

If potential new or increased adverse effects on the conservation and sustainable use of biological diversity or on human health are identified in relation to the StaEv through the above analysis of possible interactions, additional supporting data on StaEv may be required, such as:

(a) Phenotypic characteristics, including the levels of expression of any introduced gene products or modified traits, compared to the parent LMOs and to relevant non-modified recipient organisms (plants);

(b) Compositional analysis (e.g. levels of expression in the LMO and persistence and accumulation in the environment, such as in the food chain) of substances with potentially harmful effects newly produced by the StaEv, (e.g. insecticidal proteins, allergens, anti-nutritional factors, etc.) in amounts that differ from those produced by the parental LMOs or non-modified recipient organisms;

(c) Additional information depending on the nature of the combined traits. For example, further toxicological analysis of the StaEv may be required to address any combinatorial effects arising from the stacking of two or more insecticidal traits that result in a broadened target range or increased toxicity.

Also, indirect effects due to changed agricultural management procedures, combined with the use of the transgenic stacked event LMO, should be taken into consideration.

Intentional and unintentional StaEvs may have altered environmental impacts as a result of cumulative and combinatorial effects of the stacked traits prevalent in different LMOs of the same species in the receiving environment. Unintentional StaEvs may arise from outcrossing with other LMOs of the same species or cross-compatible relatives (see "Use of terms"). If a number of different StaEvs are cultivated in the same environment a number of varying unintentional StaEvs may occur. Changed impacts on non-target organisms or a change in the range of non-target organisms in the likely receiving environment should be taken into account.

Comment [s36]: Combinatorial effects are addressed in the previous example. Any recommendations on how to assess potential interactions should be captured in the same point. Care should be taken not to repeat recommendations given in the Roadmap. Stacked events do not merit any special considerations for cumulative effects. Recommend that this section be deleted.

Development of specific methods for distinguishing the combined transgenes in a stacked event from the parental LMOs *(see step 5, point to consider (d) of the Roadmap for Risk Assessment)*

Rationale:

Some of the risk management strategies for StaEvs may involve methods for the detection and identification of these LMOs in the context of environmental monitoring. Currently, many detection methods for LMOs rely on DNA-based techniques, such as polymerase chain reaction (PCR) or protein based ELISA tests targeted to single transformation events. The methods used to detect the transgene in the parental lines may not be sensitive or specific enough to differentiate between single parental transformation events and the same event being part of a stacked event. A special problem may arise particularly in the cases where the StaEv contains multiple transgenes with similar DNA sequences.

[24] See definition of combinatorial and cumulative effects in the Roadmap (footnotes 17 and 19, respectively).

~~Therefore, the detection of each and all individual transgenes in a StaEv may become a challenge and need special consideration.~~Detection and identification methods for the TraEv can be tested on the StaEv to determine if they are still suitable. If they are not found to be suitable, new detection and identification methods for the StaEv can be developed.

BIBLIOGRAPHIC REFERENCES

See references relevant to "*Risk Assessment of LMOs with Stacked Genes or Traits*":
http://bch.cbd.int/onlineconferences/stackedref_ahteg_ra.shtml

B. RISK ASSESSMENT OF LIVING MODIFIED CROPS WITH TOLERANCE TO ABIOTIC STRESS

INTRODUCTION

The aim of this document is to provide further guidance for the risk assessment of living modified (LM) crops with improved tolerance to abiotic stress.

This guidance document should be considered in the context of the Cartagena Protocol on Biosafety. The elements of Article 15 and Annex III of the Protocol also apply to LM crops with tolerance to abiotic stress. Accordingly, the methodology and points to consider[25] contained in Annex III are also applicable to this type of LMO.

The potential environmental adverse effects of an LM crop with abiotic stress tolerance depends on (i) the receiving environment; (ii) the modified crop, (iii) phenotypic changes resulting from the genotypic changes made to the plant and (iv) its intended use. A risk assessment would be performed on a case-by-case basis in accordance with Annex III of the Protocol.

This guidance document complements the Roadmap for Risk Assessment developed by the AHTEG on Risk Assessment and Risk Management, and focuses on issues that are of particular relevance to the risk assessment of LM crops tolerant to abiotic stress.

USE OF TERMS

"Abiotic stresses" are environmental conditions caused by non-living factors that are detrimental or suboptimal to the growth, development and/or reproduction of a living organism. Types of abiotic stresses include, for example, drought, salinity, cold, heat, soil pollution and air pollution (e.g., nitrous oxides, ozone).

RISK ASSESSMENT

While the same general principles used in the risk assessments of other types of LMOs also apply to LM crops with increased tolerance to abiotic stress, there are a number of specific issues that may be of particular importance when assessing the risks of LM crops tolerant to abiotic stresses.

Questions that may be relevant to the risk assessment of LM crops with tolerance to abiotic stress in connection with the intended use and receiving environment include:

- Would the tolerance trait have the potential to increase the invasiveness, persistence or weediness of the LM crop that causes adverse effects to other organisms?
- ~~Would a LM plant expressing tolerance to a particular abiotic stress have other advantages in the targeted receiving environment that cause adverse effects?~~
- Would any LMO arising from outcrossing with the abiotic stress tolerant LM crop, have the potential to colonize an ecosystem beyond the targeted receiving environment?
- Would the abiotic stress tolerance trait, for example, via pleitropic effects, have the potential to affect, *inter alia*, pest and disease resistance mechanisms of the LM crop?

Comment [s37]: It would be useful to include a discussion here as to how abiotic stress tolerant traits could have such effects.

Comment [s38]: This consideration is unclear and not be specific to abiotic stress tolerant LMOs and is captured in the Roadmap.

Comment [s39]: An LMO arising from outcrossing would be unintentional and therefore wouldn't have a targeted receiving environment.

[25] Paragraphs 8 and 9 of Annex III, respectively.

Some abiotic stress tolerance traits may~~Some of the potential adverse effects to be evaluated in the risk assessment, from the introduction of crops tolerant to abiotic stress into the environment include, for example: a)~~ confer an increased selective advantage(s) other than the intended tolerance trait. Furthermore, they could potentially result in ~~; b)~~ increased persistence in agricultural areas and increased invasiveness in natural habitats. The potential for an adverse effect to occur as a result of either of these situations should be considered for abiotic stress tolerant crops. Similarly, these factors should be considered should the novel trait be introduced into other species as a; ~~c) adverse effects on organisms exposed to the crop; and d)~~ consequences of potential gene flow to wild or conventional relatives. ~~While these adverse effects may exist regardless of whether the tolerant crop is a product of modern biotechnology or conventional breeding, some specific issues may be more relevant in the case of abiotic stress tolerant LM crops.~~

Comment [s40]: Again, a discussion here as to how this might occur with abiotic stress tolerance traits would be useful.

Comment [s41]: The basis for why abiotic stress tolerance traits are more likely to have an adverse effect on organisms exposed to the crop is not clear. Recommend that this text be deleted.

Comment [s42]: What is the basis for this statement?

Characterization of the LM crop with tolerance to abiotic stress in comparison with its ~~non-modified crop~~recipient *(see step 1 of the Roadmap for Risk Assessment)*

Rationale:

The first step in the risk assessment process involves the characterization of genotypic or phenotypic, ~~biological, intended and unintended~~ changes associated with the abiotic stress tolerant LM crop that may have adverse effects on biodiversity in the likely receiving environment, taking into account risks to human health. This step is the 'hazard identification step' in other risk assessment guidance.

The identification of genotypic and phenotypic changes in the abiotic stress tolerant LM crop, either intended or unintended, is typically done in comparison with the ~~non-modified~~ recipient organism (see step 1 of the Roadmap). The ~~non-modified~~ comparator provides the baseline information for comparison of trials when it is grown at the same time and location as the LM crop. Comparisons with the observed range of changes in the recipient ~~non-modified~~ crop in different environments, also provides baseline information.

Comment [s43]: This text is a repetition of recommendations in the Roadmap. It would be more useful to just refer readers to the Roadmap as opposed to reiterating it here.

Challenges with respect to experimental design: Abiotic stress crops may present unique challenges in experimental design for risk assessment. In some cases, for instance, an approach uses different reference plant lines, which typically include a range of genotypes representative of the natural variation in the crop species. In such conditions, choosing appropriate comparators could be a challenge and there are several proposals on whether and how the comparative approach can be used to characterize LM crops tolerant to abiotic stress in these likely receiving environments. Another important consideration is whether the experimental design properly controlled for the effect of the abiotic stress trait. In the extreme case, when the recipient ~~non-modified~~ crop has never been grown in the range of conditions of the receiving environment because the abiotic stress conditions prevent or severely affect the growth of the recipient ~~non-modified~~ crop, a comparative approach between the LM crop and the ~~non-modified crop~~recipient will need to be adjusted.

Comment [s44]: An explanation her would be useful.

Comment [s45]: It is not clear why this might be the case for abiotic stress tolerance traits.

Comment [s46]: It would be useful to provide guidance on how these adjustments can be made.

Comment [s47]: No guidance is given on how this should be done. Explain further or delete entirely.

The use of non-isogenic reference lines can make it more difficult to identify statistically meaningful differences. However, they are useful in identifying differences that are biologically meaningful. Any characteristic that is within the range measured in the reference lines is not biologically meaningful because that characteristic already exists in the environment, and therefore it is unlikely to have a new adverse effect as compared to the reference lines. In some situations when a comparator may not be available to carry out a meaningful comparison, a characterization of the abiotic stress tolerant LM crop as a novel genotype in the receiving environment may be conducted. ~~In the future, information available from "omics" technologies, for example, "transcriptomics" and "metabolomics", if available, may help to detect phenotypes (e.g., the production of a novel allergen or anti-nutrient) that cannot be detected using a comparison between field grown plants at a suboptimal condition.~~

Comment [s48]: Suggest that this text be deleted. At this time, the application of "omics" technologies to the risk assessment of LMOs suffers from many shortcomings, most notably the lack of a link between observed changes and adverse effects (see Doerrer et al. 2010. Regulatory Toxicology and Pharmacology 58: S2–S7 and Ricroch et al. 2011. Plant Physiology 155: 1752–-1761 for useful reviews). Furthermore, given that this is intended to be a living document, reference to "omics" technologies can be added at a later time if the technology has sufficiently advanced as to be informative.

Points to consider:

(a) Characteristics of the LM crop under the abiotic stress and non-stress conditions and under different stresses, if applicable; and

~~(b) Likelihood of gene flow to wild or domestic relatives; and~~

(c) Whether one or more suitable comparators are available and the possibility of their use in the appropriate experimental design.

Comment [s49]: This consideration is not unique to abiotic stress tolerance traits.

Unintended characteristics *(see step 1 of the Roadmap for Risk Assessment)*

Comment [s50]: Some of the points covered in this section are also covered in the Introduction. This redundancy should be reduced.

Rationale:

Both intended and unintended changes to the LM crop which are directly or indirectly associated with the abiotic stress tolerance that may have adverse effects should be identified. These include changes to the biology of the crop plant (e.g. if the genes alter multiple characteristics of the plant) or to its distribution range in relation to the potential receiving environment (e.g. if the plant can grow where it has not grown before), that may cause adverse effects.

The abiotic-stress-tolerant LM crop may have unintended characteristics such as tolerances to other types of biotic and abiotic stresses, which could lead to a selective advantage of these crop plants ~~under conditions other than that related to the modified trait~~. For instance, crops modified to become tolerant to drought or salinity may be able to compete better than their counterparts at lower and higher growing temperatures.

Comment [s51]: An explanation as to why this is the case would be useful.

It is also possible the LM crops with enhanced tolerance to an abiotic stress could have changes in seed dormancy, viability, and/or germination rates under other types of stresses. Particularly if genes involved in abiotic stress are also involved in crucial steps in physiology, modifications involving these genes may, therefore, have pleiotropic effects. ~~Such LM crops may also transfer genes for stress tolerance at higher frequencies than observed in non-modified crops~~.

Comment [s52]: What is the basis for this statement?

A potential mechanism for interactions between abiotic and biotic stresses may exist in plants. For example, drought or salinity-tolerant LM crops may acquire a changed tolerance to biotic stresses, which could result in changed interactions with their predators, parasitoids and pathogens, and, therefore, have both direct and indirect effects on organisms that interact with them.

Points to consider:

(a) Any intended or unintended change that may lead to selective advantage or disadvantage acquired by the LM crop under other abiotic or biotic stress conditions that could cause adverse effects;

(b) Any change in the resistance to biotic stresses and how these could affect the population of organisms interacting with the LM crop; and

~~(c) A change in the substances (e.g., toxin, allergen, or nutrient profile) of the LM crop that could cause adverse effects.~~

Comment [s53]: This consideration is not unique to plants with abiotic stress tolerance traits. Recommend that it be deleted.

Increased persistency in agricultural areas and invasiveness of natural habitats *(see steps 1, 3 and 5 of the Roadmap for Risk Assessment)*

Comment [s54]: Some of the points covered in this section are also covered in the Introduction. This redundancy should be reduced.

Rationale:

Climate ~~change~~conditions, water ~~depletion~~ availability ~~or~~and ~~elevated salt content~~soil salinity are examples of factors that limit the growth, productivity, spread or persistence of a crop. Expression of the

genes for abiotic stress tolerance could result in increased persistence of the modified crop in agricultural areas. Expression of these genes may also alter the capacity of LM crops to spread to and establish in climatic and geographic zones beyond those initially considered as the likely or potential receiving environments.

The gene(s) inserted for tolerance to, for instance, drought and salinity might also affect molecular response mechanisms to other forms of abiotic stress, such as cold temperatures. For example, when the genetic modification affects genes that also regulate key processes in seeds, such as abscisic acid (ABA) metabolism, physiological characteristics such as dormancy and accumulation of storage lipids may also be changed. In such cases, the seeds of a tolerant crop, modified for drought or salinity tolerance, may acquire in addition tolerance to cold resulting in an increased winter survivability of the seeds. Therefore, an abiotic stress-tolerant crop may acquire the potential to persist better than its conventional counterpart under different abiotic-stress conditions.

Points to consider:

(a) Consequences of the increased potential for persistency of the modified crop in agricultural habitats and consequences of increased potential for invasiveness in natural habitats;

(b) Need for control measures if the abiotic stress-tolerant crop shows a higher potential for persistency in agricultural or natural habitats, that could cause adverse effects;

(c) Characteristics that are generally associated with weediness such as prolonged seed dormancy, long persistence of seeds in the soil, germination under a broad range of environmental conditions, rapid vegetative growth, short lifecycle, very high seed output, high seed dispersal and long-distance seed dispersal; and

(d) Effects of climate change on agriculture and biodiversity and how this could change the habitat range of the LM crop in comparison to the non modified crop.

(e) If the LM crop expressing tolerance, would have a change in its agriculture practices.

BIBLIOGRAPHIC REFERENCES

See references relevant to "*Risk Assessment of LM Crops with Tolerance to Abiotic Stress*":
http://bch.cbd.int/onlineconferences/abioticref_ahteg_ra.shtml

C. RISK ASSESSMENT OF LIVING MODIFIED MOSQUITOES

INTRODUCTION

Living modified (LM) mosquitoes are being developed through modern biotechnology to reduce transmission of vector borne human pathogens, particularly those that cause malaria, dengue and chikungunya. Control, including eradication of such diseases, is a recognized public health goal. Some of the strategies being developed are to control mosquito vectors by suppressing their population or reducing their competence. These strategies can be subcategorized according to the technology involved and the method used. Some are intended to develop LM mosquitoes that are genetically modified to be sterile or self-limiting (i.e., unable to pass the modified trait on indefinitely through subsequent generations). Modern biotechnology techniques for developing sterile LM mosquitoes are different from those based on the use of irradiation to induce male sterility.

Other modern biotechnology strategies are also being used for developing LM mosquito populations that are self-sustaining or self-propagating (i.e., heritable modifications intended to spread through the target population). The strategy used is an important factor to be considered in the risk assessment and risk management process since there might be different points to be considered, depending on the specific strategy used.

The biology and ecology of mosquitoes on the one hand, and their impact on public health as vectors of human and animal diseases on the other hand, pose new considerations and challenges during the risk assessment process, which have mainly dealt with LM crop plants thus far.

This guidance document provides information for the risk assessment of environmental releases of LM mosquitoes and aims at helping to conduct risk assessments for environmental releases of LM mosquitoes. Although the focus of this guidance is on LM mosquitoes, in principle, it may also be useful for the risk assessment of similar non-LM mosquito strategies.

The main emphasis of this guidance document is the assessment of potential risks to biodiversity. Nevertheless, the potential adverse effects to human health arising from environmental releases of LM mosquitoes should also be considered.

This guidance document complements the Roadmap for Risk Assessment developed by the AHTEG on Risk Assessment and Risk Management and focuses on specific issues that may need special consideration on the risk assessment for environmental releases of LM mosquitoes.

OBJECTIVE

The objective of this document is to give additional guidance on the risk assessment (RA) of LM mosquitoes in accordance with Annex III to the Cartagena Protocol on Biosafety.[26] Accordingly, it aims at complementing the Roadmap for Risk Assessment on specific issues that may need special consideration for the environmental release of LM mosquitoes.

[26] The Parties to the Cartagena Protocol on Biosafety have mandated the AHTEG to 'develop a "roadmap", such as a flowchart, on the necessary steps to conduct a risk assessment in accordance with Annex III to the Protocol and, for each of these steps, provide examples of relevant guidance documents'. The Roadmap is meant to provide reasoned guidance on how, in practice, to apply the necessary steps for environmental risk assessment as set out in Annex III of the Protocol. The Roadmap also demonstrates how these steps are interlinked.

SCOPE

This document focuses on the specifics aspects of risk assessment of LM mosquitoes developed to be used in the control of human and zoonotic diseases such as malaria, dengue, chikungunya, yellow fever and West Nile.

ISSUES TO BE CONSIDERED IN THE RISK ASSESSMENT

(See step 1 of the Roadmap for Risk Assessment of LMOs)

Specific and comprehensive considerations should be undertaken with respect to the potential adverse effects of a particular LM mosquito, taking into account the species of the mosquito, the LM trait, the intended receiving environment, and the objective and scale of the intended release. These considerations should focus on, for instance: (a) description of the genetic modification; (b) the kinds of possible adverse effects for which there are scientifically plausible scenarios; (c) the species and ecological processes that could be affected by the introduction of the LM mosquitoes; (d) the protection goals of the country where the LM mosquitoes will be introduced; and (e) a conceptual link between the identified protection goals and the introduction of the LM mosquito into the environment.

The biology and, to some extent, the ecology of the mosquito species that transmit malaria and dengue are well known in many regions of the world. However, in certain regions and in the environment where the LM mosquito is likely be released, more information may be needed depending on the nature and scale of the LM strategy to be deployed. In many of these environments few studies have been conducted to examine gene flow among vectors, their mating behaviour, the interactions between vectors sharing one habitat, how pathogens respond to the introduction of new vectors, etc. Such information may be needed to establish a baseline in order to successfully assess the risks of LM mosquitoes. Additionally, methods for the identification of specific ecological or environmental hazards are also needed.

Effects on biological diversity (species, habitats, ecosystems, and ecosystem services)

(*See step 2 of the Roadmap for Risk Assessment of LMOs*)

Rationale:

The release of LM mosquitoes may have a negative impact on the target vector and pathogen[27] and other species, such as:

New or more vigorous pests, especially those that have adverse effects on human health: (i) the released LM mosquitoes may not function as expected, for example gene silencing or production failures could result in the release of non-sterile or competent mosquitoes and thus increase the vector population or disease transmission; (ii) the released LM mosquitoes could transmit another disease more efficiently than indigenous non-LM mosquitoes, such diseases might include yellow fever, chikungunya, etc.; (iii) suppression of the target mosquito might result in the population of another vector species to increase and result in higher levels of the target disease or the development of a new disease in humans and/or animals. These other vector species may include other mosquito vectors of other diseases; (iv) the released LM mosquitoes might become pests; (v) the released LM mosquitoes might cause other pests to become more serious, including agricultural pests and other pests that affect human activities.

Harm to or loss of other species: The released LM mosquitoes might cause other species (for instance fish that rely seasonally on mosquitoes for food) to become less abundant. These include species of ecological, economic, cultural and/or social importance such as wild food, endangered, keystone, iconic

[27] For the purpose of this guidance, the term "target vector" refers to the mosquito that transmits the disease and "target pathogen" is the disease causing agent transmitted by the target mosquito.

and other relevant wildlife species. Ecological effects might result from competitive release if the target mosquito population is reduced or from trophic consequences of species that rely on mosquitoes for food at specific times of the year. Effects may also occur if (i) the target mosquitoes transmit a disease to animal species, (ii) the released LM mosquitoes transmit a disease to animal species more efficiently, (iii) another vector of an animal disease was released from control when the target mosquito population was reduced, or (iv) the population of a target pathogen is reduced or lost and this may affect other organisms that interact with it.

Although mosquitoes, like other insects, typically have strong reproductive isolating mechanisms that will not allow interspecific gene flow, if sterile interspecific mating between released LM mosquitoes and other mosquito species should occur, it could disrupt the population dynamics of these other species, leading to harm or loss of valued ecological species. Moreover, cessation of transmission of pathogens to other animals (e.g., West Nile virus to birds, Rift Valley fever virus to African mammals) might alter the population dynamics of those species, favouring increases in their numbers.

Disruption of ecological communities and ecosystem processes: The ecological communities in the ephemeral, small aquatic habitats occupied by the non-LM mosquitoes are unlikely to be disrupted beyond the possibilities already addressed above under "harm to or loss of other species." However, if the released LM mosquitoes were to inhabit natural habitats (e.g. tree-holes), disruption of the associated community is a possibility. The released LM mosquitoes might degrade some valued ecosystem process. This might include processes such as pollination or support of normal ecosystem functioning. These processes are often referred to as "ecosystem services". However, the valued ecosystem processes may also be culturally or socially specific. Under some circumstances, mosquito species are significant pollinators. In those cases, mosquito control of any kind might reduce the rate of pollination of some plant species or cause a shift to different kinds of pollinators. Habitats in which mosquitoes are the dominant insect fauna (e.g., high Arctic tundra, tree holes) would be changed if mosquitoes were eliminated; however, the common target vector species are usually associated with human activity and therefore not as closely tied to ecosystem services.

Points to consider:

(a) Impacts on the target mosquitoes and pathogens resulting from the use of the strategy under consideration;

(b) Whether the LM mosquitoes have the potential of causing adverse effects on other species which will result in the other species becoming agricultural, aquacultural, public health or environmental pests, or nuisance or health hazards;

(c) Whether the target mosquito species is native or invasive to a given area;

(d) The habitat range of the target mosquito species and whether the habitat range is likely to be affected by climate change;

(e) Any other species (e.g. animal hosts, larval pathogens or predators of mosquitoes) in addition to the pathogen, that typically interact with the LM mosquito in the likely receiving environment;

(f) Whether the release of LM mosquitoes is likely to affect other mosquito species that are pollinators or otherwise known to be beneficial to ecosystem processes;

(g) Whether the LM mosquitoes are likely to have an adverse effect on other interacting organisms, e.g. predators of mosquitoes;

(h) Whether species replacement by other disease vector species may occur, and if so, whether it can result in an increased incidence of the target disease or new diseases in humans or animals.

Gene Flow

(*See steps 2 and 3 of the Roadmap for Risk Assessment of LMOs*)

Rationale:

With regard to the biosafety of LM mosquitoes, gene flow refers to the transfer of transgenes[28] or genetic elements from the LM mosquitoes to non-LM mosquitoes. It can occur via cross-fertilisation or other movement of the transgenes or genetic elements. Various factors may influence gene flow and any associated adverse effects, such as, the strategy, the transgenes, the gene drive system [29] and the stability of the trait(s) carried by the mosquito over generations, as well as the receiving environment, etc.

Gene flow through cross-fertilization: Some LM mosquitoes are being developed to spread the introduced trait rapidly through the target mosquito population. For instance, when introduced into *Anopheles gambiae*, the trait may be expected to spread throughout the *A. gambiae* species complex. Other LM mosquito technologies are designed to be self-limiting and, in such cases, spread of the transgenes or genetic elements in the target mosquito population is not intended or expected. For the self-limiting technologies, the potential for an unexpected spread of the introduced trait should be considered by focusing on the assumption that any management strategy to limit the spread could fail. Gene flow between different species should be considered for all of the LM mosquito technologies in spite of the fact that mosquitoes, like other insects, typically have strong reproductive isolating mechanisms that will not allow interspecific gene flow. Identifying the key reproductive isolating mechanisms and possible conditions that could lead to the breakdown of such mechanisms is of particular importance in the risk assessment of LM mosquitoes with this trait. In addition, the fitness conferred by the introduced trait and the population size and frequency of the introduction of the LM mosquito into the environment will also determine the likelihood and rate of spread of the transgenes or genetic elements.

Horizontal gene flow: For the purpose of this document, "horizontal gene flow", is the movement of genetic information from one organism to another through means other than sexual transmission. Gene drive systems for moving genes into wild populations may be the initial focus of the risk assessment. The risk of horizontal gene flow in LM mosquitoes that do not contain a gene drive system is likely to be smaller but should nevertheless be assessed on a case-by-case basis.

Persistence of the transgene in the environment. Some of the transgenes in LM mosquitoes are designed not to persist whereas others are expected to spread rapidly and/or persist through wild populations. In cases where the LM mosquitoes have been found through the risk assessment process to have the potential to cause adverse effects to the biological diversity, taking also into account human health, methods to reduce the persistence of the transgene in the environment needs to be considered

Points to consider:

(a) Whether LM mosquitoes have the potential to transfer the modified traits to wild mosquito populations (when it is not an intended strategy) and/or to non-related organisms, and if so, the occurrence of any potential undesirable consequences;

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[28] For the purpose of this document, a transgene is a nucleic acid sequence in an LMO that results from the application of modern biotechnology as described in Article 3 (i) a of the Protocol.

[29] Gene drive systems are methods of effectively introducing the desired gene into a mosquito population (Selfish DNA versus Vector-Borne Disease, Environmental Health Perspectives (2008) 116 - http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2235231/pdf/ehp0116-a00066.pdf).

(b) Whether the LM mosquitoes have the potential to induce undesirable characteristics, functions, or behaviour within the target mosquito species, other wild related species or non-related organisms;

(c) Any undesirable consequence should the transgene persist in the environment.

Evolutionary responses (especially in target mosquito vectors or pathogens of humans and animals)

(*See step 1 of the Roadmap for Risk Assessment of LMOs*)

Rationale:

Any strong ecological effect also exerts an evolutionary selection pressure on the human and animal pathogens and the mosquito vectors. The main evolutionary effects are those that could result in a breakdown in the effectiveness of the technology and the resumption of previous disease levels. Some LM mosquito strategies aim at modifying the mosquito vector's ability to transmit diseases through changes in its physiological mechanisms. An evolutionary effect resulting in the development of resistance to physiological mechanisms in the targeted pathogen might occur when modifying mosquito vector competence. This might harm the effectiveness of the strategy used and result in a population of pathogens that may be transmitted more easily by all types of vectors.

Other evolutionary effects could be hypothesized, including effects resulting from climate change, but they would first require the occurrence of some adverse effect on a species, community or ecosystem effect. Therefore, consideration of secondary evolutionary effects can be postponed until such effects are identified and found to be significant.

Points to consider:

(a) Whether the target mosquito vector has the potential to evolve and avoid population suppression, regain vector competence or acquire new or enhanced competence to another disease agent, and if so, the occurrence of any possible undesirable consequences;

(b) Whether the trait has the potential to evolve and thus lose its effectiveness, or the pathogen to evolve and overcome the limitation posed by the genetic modification, and if so, the occurrence of any possible undesirable consequences.

RISK-MANAGEMENT STRATEGIES

(*See step 5 of the Roadmap for Risk Assessment of LMOs*)

Risk assessors may want to consider risk-management strategies such as the quality control of the released LM mosquitoes and monitoring them and the environment for potential unintended adverse effects. There should also be strategies in place for halting the release and application of mitigation methods if an unanticipated effect occurs. Careful implementation of the technology including the availability of mitigations measures (such as an alternative set of control measures should a problem occur) and the integration of other population control methods should be considered. In some circumstances methods to reduce the persistence of the transgene in the environment or to mitigate adverse effects resulting from the expression of the transgene might be needed. Monitoring during and after the environmental release of the LM mosquitoes so as to address prompt detection of unexpected adverse effects may also be considered.

Points to consider:

(a) Availability of monitoring methods to:

(i) Measure the efficacy and effectiveness of LM mosquito technology;

(ii) Assess the potential evolutionary breakdown of the LM mosquito technology (monitoring for transgene stability and proper function over time);

(iii) Determine the level to which the identified adverse effects may be realized, including detection of unexpected and undesirable spread of the transgenic trait (monitor for undesirable functions or behaviours within target species and other wild related species);

(b) Availability of mechanisms to recall the LM mosquitoes and transgenes in case they spread unexpectedly (e.g. mass release of wild-type mosquitoes above a certain threshold, alternative control methods including genetic control);

(c) Availability of methods for managing the dispersal of the LM mosquitoes and ensuring that they do not establish themselves beyond the intended receiving environment (eg. vegetation-free zones, traps, high threshold gene drive systems);

(d) Availability of methods to manage potential development of resistance, e.g. in the target vector or pathogen.

OTHER ISSUES

There are other factors that may be taken into consideration in the decision for environmental releases of LM mosquitoes which are not covered by Annex III of the Protocol. They encompass, *inter alia*, social, economic, cultural and health issues associated with the application and acceptance of the technology.

BIBLIOGRAPHIC REFERENCES

See references relevant to "*Risk Assessment of LM Mosquitoes*":
http://bch.cbd.int/onlineconferences/mosquitoesref_ahteg_ra.shtml

From: Jaimie Schnell
To: Girard, Cecile
Date: 2016-02-22 12:32 PM
Subject: Re: AHTEG meeting on Friday

If 30 minutes gives us enough time, then that works for me. Thanks, Cécile. I'll talk to you on Friday.

Jaimie

>>> Cecile Girard 2016-02-22 12:31 PM >>>
Hi Jaimie
30 minutes should be enough; however feel free to suggest another day/time if Friday is becoming tight.

>>> Jaimie Schnell 2016-02-22 12:12 PM >>>
Hi Cécile,

Do you think you'll need me for the full hour on Friday to discuss the AHTEG? I am looking to fit in another meeting at 10:30 and was wondering if 30 minutes would be enough.

Thanks,
Jaimie

s.16(2)(c)

s.19(1)

From: Cecile Girard
To: Schnell, Jaimie
CC: Davis, Sarah G.; Hitchon, Andrea; Levac, Dylan
Date: 2016-02-25 4:31 PM
Subject: Re: AHTEG/ Roadmap- NEW DATE

Sorry about this, yes we'll re-book.
Take care,
Cécile

>>> Jaimie Schnell 2016-02-25 4:28 PM >>>
Hi everyone,

Unfortunately I just got news that

Could we reschedule this meeting?

Thanks!
Jaimie

>>> Cecile Girard 2016-02-15 10:31 AM >>>
to gain insight into Jaimie's work and participation in the online expert discussions on the Roadmap and the modules under it, as well as the Canadian efforts to influence the Roadmap. Thanks Jaimie!

Call-in number : (613) 960 7516
Conference ID:

s.19(1)

From:
To:
Date: 2016-03-04 1:57 PM
Subject: cellule de veille OGM # 40
Attachments: Cellule de veille OGM_Février 2016_VF.pdf

Bonjour à tous,

Veuillez trouver ci-joint, le bulletin numéro 40 de la cellule de veille OGM sous sa nouvelle formule.
Nous espérons que vous le trouverez intéressant.
Bonne lecture !

Gouvernement du Québec - MAPAQ
Direction Appui à la Recherche et à l'Innovation
200 chemin Ste-Foy, 10e étage
Québec (Qc) G1R 4X6
Tél.: (418) 380-2100 poste Fax: (418) 380-2162

https://www.agrireseau.net/nanotechnologies-bioalimentaire

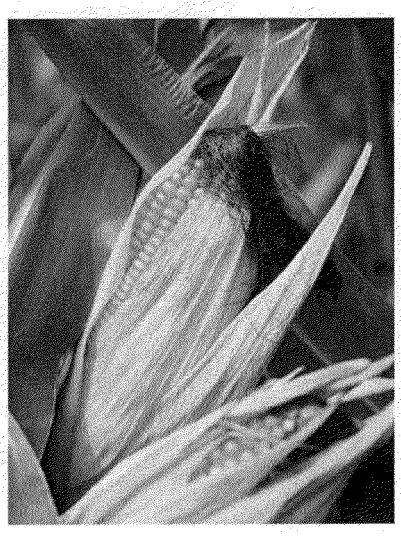
Cellule de veille OGM

NUMÉRO 40 | FÉvRieR 2016

Statistiques sur les cultures génétiquement modifiéesau Québec

Selon les nouvelles données de l Institut de la statistique du Québec, 84 % du maïs-grain ensemencé au Québec (306 500 hectares sur 365 000 au total) et 57 % du soja (180 000 hectares sur 315 000 au total) étaient génétiquement modifiés(GM) en 2015.

Outre le maïs-grain et le soja, on utilise également le canola GM au Québec. Mais depuis 2003, il n y a plus de compilation officielledes statistiques sur cette culture.



Réf éRenceS :

Superficiedes grandes cultures génétiquement modifiées,rendement à l hectare et production, par région administrative, Québec, 2015.
en ligne : http://www.stat.gouv.qc.ca/statistiques/agriculture/grandes-cultures/gc_2015gm.htm

Superficiedes grandes cultures, rendement à l hectare et production, par région administrative, Québec, 2015.
en ligne : http://www.stat.gouv.qc.ca/statistiques/agriculture/grandes-cultures/gc_2015.htm

Nouveau regard sur les études d'innocuité des organismes génétiquement modifiés

L'Union européenne finançait depuis quelques années, le projet GMO *Risk Assessment and Communication of Evidence* (GRAce). ce dernier visait à accroître la transparence et la traçabilité des informations sur les risques et les avantages potentiels associés à la dissémination volontaire des organismes génétiquement modifiés (OGM).

Un des objectifs de GRAce était d'évaluer la conception, l'exécution et l'interprétation des essais d'alimentation avec des rongeurs (90 jours et études à long terme) et des études alternatives avec des ingrédients ou des denrées complètes. cette évaluation visait à fournir des recommandations sur la pertinence de ces outils pour cerner les risques associés aux plantes génétiquement modifiées en tenant compte des forces et des limites scientifiques des différentes approches.

Les recommandations de l'équipe de GRAce sur ces points ont fait l'objet de discussions lors de la conférence finale, qui s'est tenue à Postdam en novembre 2015. Le rapport est maintenant disponible sur le site Internet du projet.

L'équipe du projet a utilisé la lignée de maïs GM MON 810 dans une étude d'alimentation de 90 jours et d'un an sur des rongeurs. elle n'a trouvé aucune preuve que la réalisation d'études d'alimentation de 90 jours avec des aliments entiers apporterait des informations additionnelles sur la sécurité de l'OGM, par rapport à l'évaluation de la composition des variétés GM et non GM. Des essais alimentaires avec les aliments complets pourraient fournir des données scientifiques supplémentaires dans les cas où il y aurait un questionnement sur les risques des cultures GM dont les phénotypes ou la composition moléculaires diffèrent par rapport aux cultures conventionnelles équivalentes.

Les résultats indiquent aussi que l'alimentation des rats avec du maïs MON 810 n'a pas entraîné d'effets indésirables.

Référence :

GRAce. *Conclusions and recommendations on animal feeding trials and alternative approaches and on the use of systematic reviews and evidence maps for GMO impact assessment.* en ligne: http://www.grace-fp7.eu/sites/default/files/GRAce_conclusions%20&Recommendations.pdf

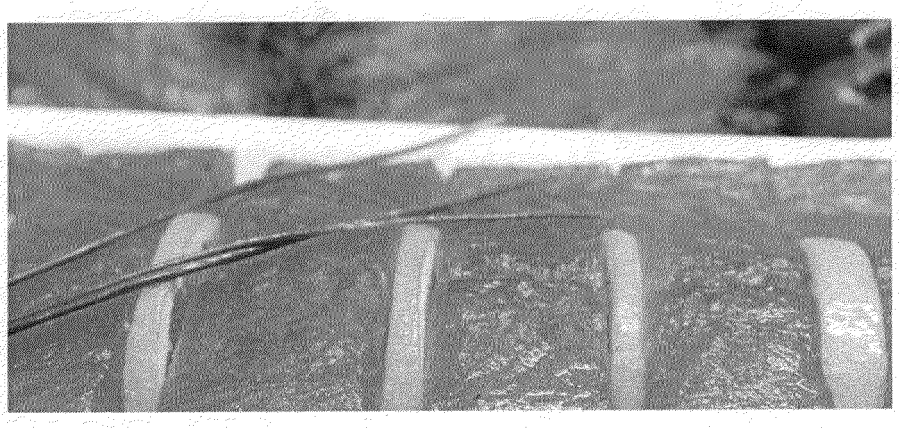
Omnibus *Spending Bill* 2016 **Interdiction de vendre** du saumon génétiquement modifié

chaque année, le congrès américain doit adopter des lois qui allouent les budgets adéquats pour toutes les dépenses publiques discrétionnaires. en règle générale, un projet de loi est adopté pour chacun des douze sous-comités du *United States House Committee on Appropriations* et du *United States Senate Committee on Appropriations*. Lorsque le congrès ne peut pas produire en temps opportun l ensemble de ces projets de loi, il peut inclure un grand nombre d entre eux et les crédits correspondants dans un seul projet de loi intitulé *Omnibus Spending Bill*.

L Omnibus Spending Bill 2016 (H.R.2029 Consolidated Appropriations Act, 2016.114th Congress [2015-2016])[1] est devenu la loi publique numéro 114-113, le 18 décembre 2015.

Une des sections de ce document concerne la commercialisation du saumon génétiquement modifié (GM), approuvé par la *Food and Drug Administration* (f DA) en novembre 2015[2]. Il y est inscrit qu au cours de l année f inancière 2016, la f DA ne doit pas permettre l introduction d aliments qui contiennent du saumon GM dans le commerce entre les états, tant qu elle n a pas publié ses lignes directrices déf initives sur l étiquetage du saumon GM et de ses produits dérivés. Rappelons que ces lignes directrices étaient soumises pour commentaires jusqu à la f in de janvier dernier[3].

L alerte à l importation de la f DA (n° 99-40)[4] en ce sens a été publiée le 29 janvier 2016.



Réf éRenceS :

1. Le texte de l *Omnibus Spending Bill* 2016 est disponible en ligne au https://www.congress.gov/bill/114th-congress/house-bill/2029/text

2. Voir l article sur l approbation du premier saumon GM aux états-Unis : *Cellule de veille OGM*, bulletin n 39, décembre 2015, page 1.

3. *Labeling Food Containing Ingredients Derived from Genetically Engineered Sources*, draf t guidance, disponible en ligne au http://www.f da.gov/forconsumers/consumerUpdates/ucm472487.htm#2

4. U.S. f ood and Drug Administration. *Import Alert 99-40 GENETICALLY ENGINEERED (GE) SALMON*, http://www.accessdata.f da.gov/cms_ia/importalert_1152.htm

Le « pipeline » mondial de cultures génétiquement modifiées jusqu'en 2020

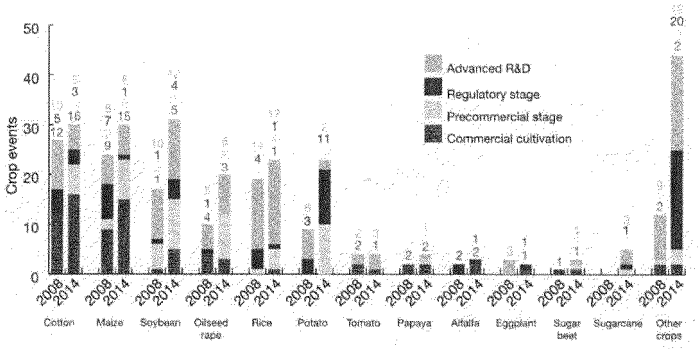
En 2014, le nombre d'hectares de cultures génétiquement modifiées (GM) dans le monde s'élevait à 181,5 millions. En 2008, l'*European Commission's Joint Research Center* (JRC) a analysé le « pipeline » des cultures GM pouvant atteindre le marché en 2015. Celui-ci était alors dominé par le soja, le coton, le maïs et le canola GM modifiés pour acquérir une tolérance à un herbicide ou une résistance à un insecte. Ces cultures étaient produites principalement par des multinationales de pays industrialisés. En janvier 2016, l'équipe de Claudia Parisi au JRC a publié, dans la revue *Nature Biotechnology*, une mise à jour de cette liste de cultures en mettant l'accent sur ce qui était présent en 2014 et qui devrait donc se trouver sur le marché en 2020.

À la lumière de données publiques et de données provenant d'agences de réglementation, les auteurs estiment qu'en 2014, on cultivait commercialement 49 plantes GM. De plus, 53 avaient atteint le stade précommercial, 43 avaient franchi le stade d'évaluation réglementaire et au moins 77 étaient rendues aux étapes avancées de la recherche et du développement. Le graphique ci-contre donne plus de détails à ce sujet.

Si la même dynamique se maintient pour la période 2014-2020, les auteurs prévoient que 219 types de cultures GM pourraient être autorisés. Parmi eux, 96 se rendront au stade de cultures commerciales.

Le paysage des plantes GM qui sont cultivées commercialement ou qui ont atteint l'étape de la précommercialisation continue d'être dominé par quatre grandes cultures, soit le maïs, le coton, le soja et le canola, comme c'était le cas pour le « pipeline » de 2008. Le riz et la pomme de terre sont ensuite les plantes les plus susceptibles de s'ajouter à l'offre commerciale. De la luzerne tolérante à un herbicide ainsi qu'une aubergine et un peuplier chinois résistants aux insectes font également partie des cultures qui pourraient prendre de l'importance. Une fève brésilienne résistante au virus et une canne à sucre indonésienne tolérante à la sécheresse devraient également arriver au stade précommercial.

Cultures GM en 2008 et 2014 de l'arrière et développement jusqu'au stade commercial



Source : Adapté de Parisi, C., et *al. (2016)*.

La tolérance à un herbicide et la résistance aux insectes demeurent les traits agronomiques que l on améliore principalement. Toutef ois, on travaille peu à peu à l amélioration d autres traits comme la résistance aux virus, la tolérance aux stress abiotiques (par exemple, la sécheresse) et l augmentation du rendement. Parmi les plantes GM tolérantes aux herbicides, on note également des changements de cible. Outre les tolérances connues au glyphosate et au gluf osinate, on observe maintenant des tolérances aux sulf onylurées, au 2,4-D, au dicamba, au isoxaf lutolæt à l oxynile.

en ce qui concerne les résistances aux insectes, on continue à cibler les f amilles des lépidoptères et des coléoptères, mais des approches alternatives avec de nouveaux gènes de *Bacillus thuringiensis* sont adoptées.

Les plantes « biof ortif iées» avec des contenus nutritionnels modif iéssont également présentes dans le « pipeline », notamment pour augmenter la quantité d omega-3 ou de vitamines. Les traits GM de qualité qui servent à des f ins industrielles sont dictés par la recherche de meilleures sources de biomasse pour les combustibles liquides et les bioproduits industriels.

comme auparavant, la plupart des compagnies qui mettent au point des cultures GM commerciales sont des multinationales dont le siège social est aux états-Unis ou en europe. néanmoins, les auteurs notent un plus grand nombre de nouvelles petites entreprises privées, notamment aux états-Unis, en Asie, en Inde et en chine, qui promeuvent leurs produits.

Réf éRence :

Parisi, c., et *al. (2016).The global pipeline of GM crops out to 2020.* nature Biotechnology 34 (1) :31-36.

deuxième génération de pommes de terre génétiquement modifiées innate® approuvée aux États-unis

en janvier 2016, la *Food and Drug Administration* (f DA) a terminé son évaluation de la deuxième génération de pommes de terre Innate® de la compagnie J. R. Simplot. elle a conclu que la composition des pommes de terre génétiquement modif iées(GM) Russet Burbank Generation 2 n est pas sensiblement dif f érente de celle de toute autre pomme de terre actuellement sur le marché. La deuxième génération de pommes de terre Innate® présente quatre avantages pour les producteurs, les transf ormateurs et les consommateurs : réduction des ecchymoses et des taches noires; diminution du niveau d asparagine; résistance au mildiou et augmentation de la durée d entreposage au f roid.

Réf éRence :

Innate® Second Generation Potato Receives FDA Safety Clearance, http://www.simplot.com/news/innate_second_generation_potato_receives_f da_saf ety_clearance

La transgénèse 2.0 avec CRISPR/Cas9: multiples **modifications génétiques** et édition du génome sans laisser de traces

Outre la possibilité de modifier le génome de n'importe quelle espèce, plus facilement et à moindre coût qu'avec les techniques précédentes, le système CRISPR/Cas9 a permis le développement d'approches inédites en ingénierie génétique dont les retombées sont loin de se limiter à la sphère universitaire.

CRISPR et l'ingénierie génétique porcine : des enjeux biomédicaux et agroalimentaires

Des chercheurs de l'université Harvard ont utilisé cRISPR/cas9 pour inactiver les 62 copies d'un gène nécessaire à la transmission de rétrovirus dans des cellules hépatiques porcines en culture. cette modification permet de réduire drastiquement la transmission du virus à des cellules humaines *in vitro*. La présence chez le porc de ces rétrovirus endogènes potentiellement transmissibles à l'homme est l'un des obstacles au développement de techniques visant à utiliser des organes de porcs pour des greffes chez l'humain. La preuve de concept *in vitro* de la modification de toutes les copies d'un gène constitue donc un progrès remarquable, même si l'efficacité de cette technique dans l'organisme reste à démontrer.

Le virus du syndrome reproducteur et respiratoire porcin (SRRP) a été détecté aux états-Unis pour la première fois en 1987. Il constitue une des plus importantes maladies sur le plan économique pour l'industrie du porc en Amérique du nord. Les vaccins produits jusqu'ici ne permettent pas de bien contrôler la maladie. Une équipe de chercheurs de l'Université du Missouri et du Kansas State University a travaillé sur la conception d'une espèce de porcs dont la génétique est modifiée à l'aide de la technologie cRISPR/cas9. Dans les dernières années, les recherches ont suggéré que chez le porc, le récepteur cD163 permettrait l'entrée du virus SRRP. L'équipe avait donc formulé l'hypothèse qu'un porc génétiquement modifié pour ne pas avoir de récepteur cD163 serait immunisé contre le SRRP. Ainsi, les chercheurs ont conçu des porcs avec différentes mutations de l'ADn correspondant au récepteur cD163 (allant de courtes mutations au retrait global du gène). Après avoir injecté le virus SRRP par voie musculaire et nasale aux porcs, l'équipe a montré que les porcs sans récepteur cD163 n'avaient aucun symptôme de la maladie, et on ne notait aucun autre changement dans leur développement.

Références :

1. Adapté du *Bulletin de veille Science, Technologie et Innovation* de Mission pour la Science et la Technologie de l'Ambassade de france aux états-Unis, publié le vendredi 18 décembre 2015. en ligne : http://www.france-science.org/La-transgenese-2-0-avec-cRISPR.html?mc_cid=8d640a6d02&mc_eid=68a6722467#nb1
2. Voir l'article « L'outil cRISPR/cas9 ouvre la voie à la modification génétique de population sauvage », *Cellule de veille OGM*, nº 39, décembre 2015.
3. YAnG, L., et *al. (2015). Genome-wide inactivation of porcine endogenous retroviruses (PERVs)*, Science 350 (6264): 1101-1104.
4. WHITWORTH, K.M., et al. (2016). *Gene-edited pigs are protected from porcine reproductive and respiratory syndrome virus.* nature Biotechnology 34(1) :20-22

CRISPR et l'inactivation de copies multiples de gènes chez des plantes cultivées

en agronomie, le système cRISPR/cas9 est utilisé depuis quelques années déjà dans plusieurs pays, pour modifier génétiquement *Arabidopsis thaliana*, un modèle majeur en biologie végétale, ainsi que des variétés de riz, de tabac, de blé, de sorgho, de maïs, de tomate, d'orange, etc. La modification simultanée de plusieurs copies de gènes avec cRISPR/cas9 est particulièrement intéressante, car de nombreuses espèces cultivées ont connu des épisodes de duplication du génome et possèdent plusieurs copies de chaque gène. Une équipe de chercheurs de l'académie chinoise des sciences a réussi, à l'aide de l'outil cRISPR/cas9, à inactiver simultanément les différentes copies d'un gène de susceptibilité au mildiou présent trois fois dans le génome d'une variété de blé, ce qui fait six modifications au total (un allèle paternel et un allèle maternel pour chaque gène).

cette stratégie d'inactivation des gènes de susceptibilité à certaines pathologies permettrait de limiter l'utilisation de fongicides et de pesticides. Si une telle approche n'est pas nouvelle, la facilité relative et la rapidité avec laquelle l'outil cRISPR/cas9 permet sa mise en place encouragent fortement son développement.

Édition du génome et obtention de plantes « éditées » identiques à des plantes naturelles

L'édition de gènes offre la possibilité de modifier des traits essentiels pour stimuler les rendements et la qualité nutritionnelle des cultures vivrières, et pour rendre les plantes plus résistantes aux parasites ou aux conditions climatiques extrêmes.

Des chercheurs chinois et britanniques ont publié en 2015 des résultats démontrant qu'il est possible, pour des espèces de riz et d'orge[8], de modifier des gènes grâce à cRISPR/cas9, d'introduire cet outil au moyen d'un transgène qui ne s'intègre pas au génome et de le voir disparaître dans les générations suivantes. Les plantes « éditées » ainsi produites transmettent la modification génétique à leur descendance et ne présentent aucune trace génétique de cette intervention. elles ne diffèrent pas des plantes présentant une variation naturelle dans l'un de leurs gènes et soulèvent donc des questions majeures en ce qui a trait à l'applicabilité de certaines réglementations.

Les agences réglementaires doivent se pencher sur la question de savoir si les plantes « éditées », c'est-à-dire celles qui ont été modifiées avec cRISPR/cas9, doivent être soumises aux mêmes réglementations que les organismes génétiquement modifiés.

Références (suite) :

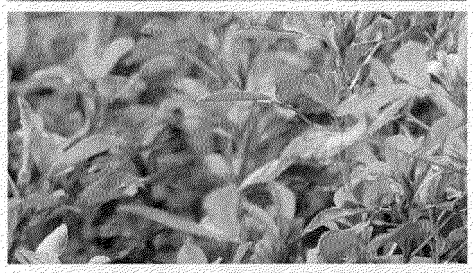
5. JIAnG, W., et *al.* (2013). *Demonstration of CRISPR/Cas9/sgRNA-mediated targeted gene modification in Arabidopsis, tobacco, sorghum and rice.* nucleic Acids Research 41(20) : e188.

6. WAnG, Y., et *al.* (2014). *Simultaneous editing of three homoeoalleles in hexaploid bread wheat confers heritable resistance to powdery mildew.* nature Biotechnology 32, p. 947-951.

7. XU, R-f, et *al.* (2015). *Generation of inheritable and "transgene clean" targeted genome-modified rice in later generations using the CRISPR/Cas9 system.* nature Scientific Reports 5 (article nº 11491). en ligne : http://www.nature.com/articles/srep11491

8. LAWRenSOn, T., et *al.* (2015). *Induction of targeted, heritable mutations in barley and Brassica oleracea using RNA-guided Cas9 nuclease.* Genome Biology 16(258) :13 pages. en ligne : http://genomebiology.biomedcentral.com/articles/10.1186/s13059-015-0826-7

Transfert de pollen entre la luzerne génétiquement modifiéeet la luzerne sauvage aux États-unis



La luzerne (*Medicago sativa subsp. sativa*) est une culture pérenne qui peut subir une pollinisation croisée par les insectes. Une équipe de chercheurs américains associés au *USDA Agricultural Research Service* a recueilli des données sur la luzerne sauvage dans les principales zones de production de semences de luzerne de l ouest des états-Unis. Ses travaux visaient à évaluer si les plantes transgéniques sauvages disséminent leurs transgènes ainsi qu à déterminer les f acteurs environnementaux et les f acteurs de production agricole inf luençanla distribution de la luzerne sauvage et de la luzerne transgénique. Les bords de routes à f resno, en calif ornie, canyon, Idaho et Walla Walla dans l état de Washington ont été scrutés en 2011 et 2012 pour vérif ier la présence de plantes sauvages. Des échantillons ont été analysés pour détecter la protéine cP4 ePSPS, qui permet une résistance au glyphosate. Les plantes sauvages ont été observées dans 404 des 4580 sites étudiés. Un peu plus du quart (27 %) de ces sites abritaient des plantes transgéniques. La f réquence des sites ayant des plantes sauvages transgéniques varie parmi les zones d étude. Des plantes transgéniques ont été trouvées dans 32,7 %, 21,4 % et 8,3 % des sites de plantes sauvages à fresno, à canyon et à Walla Walla, respectivement. cependant, d autres recherches sont nécessaires pour bien conf irmerle patron des f luxde transgènes.

Réf éRence :

Greene SL, et *al. (2015) Occurrence of Transgenic Feral Alfalfa (Medicago sativa subsp. sativa L.) in Alfalfa Seed Production Areas in the United States.* PLoS One 10 (12) : e0143296. doi:10.1371/journal. pone.0143296

initiative privée de Campbell concernant l'**étiquetage** des organismes génétiquement modifiés

Le 7 janvier 2016, le fabricant *Campbell Soup Compagny* a annoncé sa décision de divulguer la présence d'ingrédients génétiquement modifiés (GM) dans ses produits, notamment pour le maïs, le soja et la betterave à sucre. comme la science indique que la valeur nutritive des aliments issus de plantes GM n'est pas différente de celle des autres aliments, campbell continue de reconnaître que les organismes génétiquement modifiés (OGM) sont sans danger.

campbell approuve l'obligation d'étiqueter, à l'échelle nationale, les produits qui peuvent contenir des OGM. elle demande aussi au gouvernement fédéral américain d'établir une norme nationale pour les mentions « sans OGM » qui figurent sur les emballages alimentaires. Dans son communiqué, campbell souligne qu'elle a toujours pensé que les consommateurs ont le droit de savoir ce qui se trouve dans leur nourriture. Par souci de transparence, l'entreprise discutera ouvertement des ingrédients utilisés, y compris ceux qui proviennent de cultures GM, sur son site Internet « Whatsinmyfood.com ».

campbell soutient la mise en place d'une norme nationale et a contesté l'approche « état par état ». elle a travaillé avec la *Grocery Manufacturers Association* pour bloquer plusieurs initiatives de vote dans des états. campbell croit aussi qu'une approche fragmentaire état par état est incomplète et peu pratique, et que sa mise en œuvre est coûteuse pour les fabricants d'aliments. Plus important encore, la compagnie pense que cette approche est une source de confusion pour les consommateurs.

Pour l'instant, les produits portant de telles étiquettes ne devraient être offerts que sur le marché américain.

Référence :

http://www.campbellsoupcompany.com/newsroom/news/2016/01/07/labeling/ et

http://investor.campbellsoupcompany.com/phoenix.zhtml?c=88650&p=irol-newsArticle&ID=2127542 et

http://www.nytimes.com/2016/01/08/business/campbell-labels-will-disclose-gmo-ingredients.html

s.19(1)

Nouvelles brèves

ÉTude iTAlieNNe ReTiRÉe eN JANvieR 2016

Une étude de Federico Infascelli de l Université de naples décrivant des expériences sur des chevreaux nés de mères nourries au soja GM et concluant que des fragments du gène étranger peuvent être transportés à travers l intestin et sécrétés dans le lait est retirée pour falsification de données.

http://www.the-scientist.com/?articles.view/articleNo/45113/title/GM-Paper-flagged-by-Politician-Retracted/

ABBOTT, Alison. *Italian papers on genetically modified crops under investigation.* nature 529 : 268-269, 18 janvier 2016, doi:10.1038/nature.2016.19183

PReMieR CHAMP d ObSeRvATiON de POMMeS de TeRRe GÉNÉTiQueMeNT MOdiFiÉeS RÉSiSTANTeS Au Mil diOu eN OuGANdA

Le premier essai sur le terrain de pommes de terre génétiquement modifiées(GM) résistantes au mildiou mené en Ouganda d octobre 2015 à janvier 2016 a été effectué à l Institut Kachwekano Zonal près de Kabale. Douze pommes de terre GM des variétés Desiree et Victoria de l *International Potato Center* ont montré une grande résistance par rapport aux plantes non transgéniques des mêmes variétés.

Crop Biotech Update, 27 janvier 2016

NOuvel l e SeCTiON SuR l e SiTe www.OGM.GOuv.QC.CA

en raison de l approbation de la commercialisation du premier poisson transgénique aux états-Unis, la source d information gouvernementale sur les OGM modifiées onglets sur son site Web.

http://www.ogm.gouv.qc.ca/utilisation_actuelle/animaux_ogm.html

l e MARCHÉ deS biOTeCHNOl OGieS AGRiCOl eS devRAiT dOubl eR d iCi 2019

Une nouvelle étude publiée par *Transparency Market Research et intitulée Agricultural Biotechnology Market Global Industry Analysis, Size, Share, Growth, Trends and Forecast*, 2013-2019 rapporte que le marché mondial de la biotechnologie agricole valait 15,3 milliards de dollars en 2012 et qu il devrait doubler d ici 2019. Selon le rapport, la population mondiale croissante et la demande pour les biocarburants conduisent à l augmentation de la demande pour des produits génétiquement modifiés.

http://www.transparencymarketresearch.com/pressrelease/agricultural-biotechnology-market.htm

Pour de plus amples renseignements sur le contenu de ce bulletin ou pour transmettre des informations ou des commentaires, vous pouvez vous adresser à :

Direction de l appui à la recherche et à l innovation

200, chemin Sainte-Foy, 10e étage
Québec (Québec) G1R 4X6

418 380-2100, poste 7
418 380-2162

Soyez deS nôtReS à la PROchaine

Cellule de veille OGM

s.16(2)(c)

Jaimie Schnell - AHTEG/ Roadmap- NEW DATE

From: Cecile Girard
To: Davis, Sarah G.; Girard, Cecile; Hitchon, Andrea; Levac, Dylan; NHQ-...
Date: 2016-03-21
Time: 2:00 PM - 2:30 PM
Subject: AHTEG/ Roadmap- NEW DATE
Place: NHQ-AC_Skyline_T1-0-217

to gain insight into Jaimie's work and participation in the online expert discussions on the Roadmap and the modules under it, as well as the Canadian efforts to influence the Roadmap. Thanks Jaimie!

Call-in number : (613) 960 7516
Conference ID:

From: PSS-SSV Plant Science Scan/Survol Science des Végétaux
To: PSS-SSV Plant Science Scan/Survol Science des Végétaux
Date: 2016-04-05 8:20 AM
Subject: Plant Science Scan/Survol science des végétaux
Attachments: CFIA_ACIA_-_#7927043_-_vR_-_Plant_Science_Scan_Edition_15_April_2016.DOC.DRF; CFIA_ACIA_-_#7926973_-_vR_-_Survol_des_végétaux_édition_15_avril_2016.DOC.DRF; Plant Science Scan Edition 15 April 2016.pdf; Survol science des vegetaux edition 15 avril 2016.pdf

The Plant Science Scan is a compilation of publicly available information on issues of potential regulatory significance to the CFIA's Plant program. It provides readers with a brief summary and references for recently released information on regulated and emerging plant pests and diseases, invasive plant species and issues relating to Plants with Novel Traits (PNTs) and biotechnology.

In previous years similar Plant program related information has been distributed via the "Science Scan", "Science Intelligence Reports" and the "Plant Health Early Warning System" (PHEWS). As in the past, the Plant Science Scan is intended to be informational, communicating emerging scientific and technical information relevant to the CFIA's Plant program.

Receipt of this email indicates that you are currently subscribed to receive the electronically circulated Plant Science Scan. Should you wish to be removed from this Plant Science Scan distribution list, or should you be receiving this as a forwarded email and wish to be added to the distribution list, please send an email indicating your preference to PSS-SSV@inspection.gc.ca

Le Survol - science des végétaux est une compilation de renseignements publics sur des dossiers pouvant avoir de l'importance au chapitre de la réglementation pour le programme des végétaux de l'ACIA. Il fournit aux lecteurs un résumé des renseignements récents sur les maladies et les phytoravageurs réglementés et émergents ainsi que sur les espèces végétales envahissantes, en plus des références connexes. Le Survol traite également des végétaux à caractères nouveaux (VCN) et de la biotechnologie.

Au cours des années précédentes, des renseignements similaires sur le programme des végétaux ont été diffusés par l'entremise du 'Compte Rendue Scientifique', du 'Science Intelligence Reports' et du 'Plant Health Early Warning System' (PHEWS). Comme dans le passé, le Survol - science des végétaux est préparé à titre informatif et vise à communiquer de nouveaux renseignements scientifiques et techniques pertinents quant au programme des végétaux de l'ACIA.

Si vous avez reçu le présent courriel, cela signifie que vous figurez sur la liste des personnes qui reçoivent par voie électronique le Survol - science des végétaux. Si vous souhaitez retirer votre nom de la liste de distribution ou si, au contraire, ce courriel vous est transféré et que vous souhaitez ajouter votre nom à la liste de distribution, veuillez envoyer un courriel à l'adresse PSS-SSV@inspection.gc.ca en indiquant votre préférence.

Brittany Day
Plant Research & Strategies

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PLANT SCIENCE SCAN

ISSN 2369-4254

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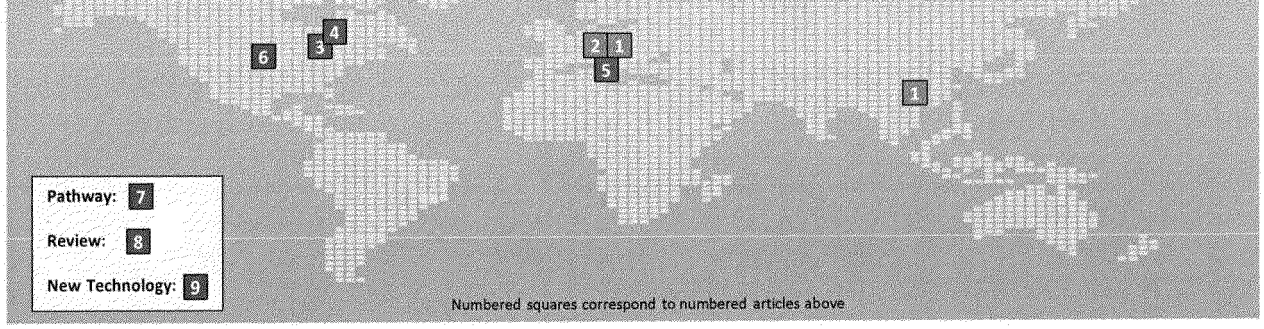
BACKGROUND: The Plant Health Science Division of the Canadian Food Inspection Agency routinely scans external sources to identify information that might be of possible regulatory significance or interest to Canada's national plant health. This Plant Science Scan report was prepared by the Canadian Food Inspection Agency's staff as a mechanism to highlight potential items of interest, raise awareness and share significant new information related to plant health.

Index of Articles



Numbered squares correspond to numbered articles above

Canadian Food Inspection Agency | Agence canadienne d'inspection des aliments

Canada

Pathology

1 New pest: New canker disease on poplar in Europe and Asia

In 2009, a new disease was observed on poplar (*Populus x euramericana*) trees in Hungary. The primary symptom of the disease was vertical cracks in the bark of the tree with a sticky, brown substance oozing from the canker. A bacterium was isolated from the ooze and named *Lonsdalea quercina* subsp. *populi* (Tóth et al., 2013). A paper in the journal *Plant Disease* reports that this bacterium has now also been identified on *Populus x euramericana* in China. Affected trees had symptoms of bark canker with frothy white exudates, and severely affected trees even died (Li et al., 2014).

A closely related species, *Lonsdalea quercina* subsp. *quercina*, has been identified as the causal agent of 'drippy nut disease' in oak in the USA (Brady et al., 2012). No records can be found in the scientific literature to suggest that either bacterium is present in Canada.

SOURCES: Brady C.L., Cleenwerck I., Denman S., Venter S.N., Rodríguez-Palenzuela P., Coutinho T.A. and De Vos P. (2012) Proposal to reclassify *Brenneria quercina* (Hildebrand & Schroth 1967) Hauben *et al*. 1999 into a novel genus, *Lonsdalea* gen. nov., as *Lonsdalea quercina* comb. nov., descriptions of *Lonsdalea quercina* subsp. *quercina* comb. nov., *Lonsdalea quercina* subsp. *iberica* subsp. nov., and *Lonsdalea quercina* subsp. *britannica* subsp. nov., emendation of the description of the genus *Brenneria*, reclassification of *Dickeya dieffenbachiae* as *Dickeya dadantii* subsp. *dieffenbachiae* comb. nov., and emendation of the description of *Dickeya dadantii*. International Journal of Systematic and Evolutionary Microbiology 62: 1592–1602.

Li, Y., He, W., Ren, F., Guo, L., Chang, J., Cleenwerck, I. Ma, Y. and Wang, H. (2014) A Canker Disease of *Populus x euramericana* in China caused by *Lonsdalea quercina* subsp. *populi*. Plant Disease 98(3): 368-378 DOI 10.1094/PDIS-01-13-0115-RE.

Tóth, T., Lakatos, T. and Koltay, A. (2013) *Lonsdalea quercina* subsp. *populi* subsp. nov., isolated from bark canker of poplar trees. International Journal of Systematic and Evolutionary Microbiology 63: 2309-2313 DOI 10.1099/ijs.0.042911-0.

2 Update: '*Candidatus* Phytoplasma prunorum' (European stone fruit yellow) in apricot orchards in the Czech Republic

A recent study provides an update on the status of '*Candidatus* Phytoplasma prunorum' (European stone fruit yellow) in the Czech Republic where the disease was reported more than 15 years ago. Long-term monitoring of '*Candidatus* Phytoplasma prunorum' in orchards concludes that the disease is an increasing concern for growers. A 50% infection level and an average of 30% of tree die-off (up to 40% in young trees) are reported in apricot orchards even when certified trees are being planted. Although disease symptoms are quite variable, chlorotic leaf-roll was the most common symptom observed in apricots during this study.

'*Candidatus* Phytoplasma prunorum' is known to be present in most European countries and causes important losses in apricot, peach and Japanese plum. It is considered a quarantine pest to Canada.

SOURCE: Nečas, T., Ondrásek, I. and Krska, B. (2015) 'Candidatus Phytoplasma prunorum' (European stone fruit yellow) - a pathogen spreading uncontrollably in apricot orchards in the Czech Republic. Acta Hortic 1105: 131-136 DOI: 10.17660/ActaHortic. 2015.1105.19.

Entomology

3 Update: Ash tree resistance to the emerald ash borer

The emerald ash borer (EAB), *Agrilus planipennis* (Coleoptera: Buprestidae), is a regulated quarantine pest for Canada, present so far only in parts of Ontario and eastern Quebec. Prohibitions on the movement of ash material and firewood have been implemented to slow the spread of the pest and 'buy time' so that studies researching host resistance of ash to EAB might evolve to a point where treatments are available that could further hinder the pests' movement or save high-value trees.

Villari et al. (2016) recently reviewed the current literature to analyze mechanisms underlying inter- and intraspecific variation in ash resistance to EAB. The review made the following conclusions:

- Manchurian ash is less preferred for adult feeding and oviposition than susceptible North American species and more resistant to larval feeding (Chakraborty et al., 2014; Rigsby et al., 2014).
- Drought stress decreased the resistance of Manchurian ash, but had no effect on constitutive bark phenolics, suggesting that they do not contribute to increased susceptibility in response to drought stress (Chakraborty et al., 2014).
- Application of methyl jasmonate was associated with increased bark concentrations of verbascoside, lignin and/or trypsin inhibitors which decreased larval survival and/or growth in bioassays, suggesting that green, white and black ash possess potential for resistance that is not expressed under natural conditions (Whitehill et al., 2014).

The authors also point to an intriguing find that a very small proportion of green ash have survived in heavily EAB-attacked stands and suggest that these 'lingering ash' could provide material to study resistance traits. A recent study by Koch et al. (2015) investigated intraspecific variation in the 'lingering ash' referred to in an effort to identify specific traits or phenotypes that are likely to be associated with increased ability to survive EAB infestation. Three selections were significantly less preferred for adult feeding, but no specific leaf volatile was associated with reduced preference, and two selections had significant differences in larval development. The results indicate that more than one mechanism is likely responsible for providing resistance in certain ash trees. Koch et al. (2015) suggest continued monitoring and preservation of ash trees that fit the criteria of the 'lingering ash' which could lead to the identification of additional EAB-resistant selections of North American ash species and sources of resistance genes for breeding programs.

SOURCES: Chakraborty, S., Whitehill, J.G.A., Hill, A.L., Opiyo, S.O., Cipollini, D., Herms, D.A. and Bonello, P. (2014) Effects of water availability on emerald ash borer larval performance and phloem phenolics of Manchurian and black ash. Plant, Cell and Environment 37: 1009-1021.

Koch, J.L., Carey, D.W., Mason, M.E., Poland, T.M., and Knight, K.S. (2015) Intraspecific variation in *Fraxinus pennsylvanica* responses to emerald ash borer (*Agrilus planipennis*). New Forests 46: 995-1011.

Villari, C., Herms, D. A., Whitehill, J. G., Cipollini, D. and Bonello, P. (2016) Progress and gaps in understanding mechanisms of ash tree resistance to emerald ash borer, a model for wood-boring insects that kill angiosperms. New Phytologist 209: 63-79.

Whitehill, J.G.A., Rigsby, C.M. Cipollini, D., Herms, D.A., Bonello, P. (2014) Decreased emergence of emerald ash borer from ash treated with methyl jasmonate is associated with induction of general defense traits and the toxic phenolic compound verbascoside. Oecologia 176: 1047-1059.

4 New Pest: *Agrilus ribesi* goes undetected in North America for a century

The Eurasian species *Agrilus ribesi* was recently reported for the first time from North America (Jendek et al., 2015) and proposed to have caused damage to currants (*Ribes* spp.) in Ontario, previously ascribed to *A. cuprescens* (Garlick, 1940). The discovery was triggered by Garlick's record of black currant, red currant and gooseberry as host plants of *A. cuprescens* in Ontario which were refuted as such in the more recent list of verified host plants (Jendek, 2003; Jendek and Poláková, 2014). The biology of *A. cuprescens,* a notorious pest of *Rubus* and *Rosa,* is well documented, while its development in *Ribes* had never been confirmed, signalling the need for record re-evaluation. All specimens of *A. cuprescens* in the Canadian National Collection were critically examined and 16 of them were re-identified as those of *A. ribesi*.

Morphological diagnostic characters for the two *Agrilus* species are provided in the recent report (Jendek et al., 2015) and complemented with DNA barcodes for four alien *Agrilus* species established in North America (i.e., *A. ribesi, A. cuprescens, A. planipennis* and *A. sulcicollis*) to enable DNA-based identification. Low genetic variability of the North American populations of *A. cuprescens* and *A. ribesi* could indicate a single introduction to North America for each of these species.

SOURCES: Garlick, W.G. (1940) Notes on the rose stem girdler, *Agrilus communis rubicola* Abeille. Canadian Entomologist 72: 21-23.

Jendek, E. (2003) Revision of *Agrilus cuprescens* (Ménétriés, 1832) and related species (Coleoptera: Buprestidae). Zootaxa 317: 1-22.

Jendek, E., Grebennikov, V. and Bocak, L. (2015) Undetected for a century: Palaearctic *Agrilus* Schaefer (Coleoptera: Buprestidae) on currant in North America, with adult morphology, larval biology and DNA barcode. Zootaxa 4034(1): 112-126.

Jendek, E. and Poláková, J. (2014) Host plants of world *Agrilus* (Coleoptera: Buprestidae). A critical review. Springer, Berlin, 706 pp.

5 *Bactra bactrana*, a sedge-feeding leafroller, attacking greenhouse sweet peppers

A recent bulletin reports *Bactra bactana* (Lepidotpera: Tortricidae) attacking sweet peppers, *Capsicum annuum*, for the first time (Roditakis et al., 2015). The infestation was detected in two greenhouses in Southern Crete, Greece, where moth larvae caused typical symptoms of a fruit borer, including small holes on the surface of the peppers and internal damage due to feeding activity. Based on the observed infestation levels of 30% and 15% of fruit in the two greenhouses, *B. bactana* could be considered a potential pest of sweet pepper. Unknown factors are expected to have facilitated the major host shift as the moth coexists with peppers in other parts of Europe without causing damage.

Species from this genus have been used for the control of weeds. This find highlights the need for extensive host plant testing when considering the release of biocontrol agents. Although some associations cannot be predicted, host plants of clear economic value should be considered for inclusion in these tests, even if the range of known hosts of a control agent is narrow.

SOURCE: Roditakis, E., Morin, S. and Baixeras, J. (2015) Is *Bactra bactrana* (Kennel, 1901) a novel pest of sweet peppers? Bulletin of Entomological Research 1-7 DOI:10.1017/S00074853150 00917.

Botany

6 First Report: *Orobanche* species parasitizing commercial sunflowers in the U.S.

In September 2014, *Orobanche ludoviciana* (Louisiana broomrape) was found parasitizing the roots of sunflower plants in a commercial sunflower production field in Kimball County, Nebraska. It was the first report of any *Orobanche* species parasitizing commercial sunflowers in the western hemisphere.

Orobanche species are obligate parasitic plants that establish vascular connections to roots of host plants from which they draw nutrients and water. *Orobanche cumana* is a well-known widespread and economically damaging pest of sunflowers in Europe. The species in question, *O. ludoviciana,* is native to North America and is widely dispersed in the Great Plains region. In Canada, it is found in southern British Columbia and the Prairie Provinces and is known to parasitize other members of the Asteraceae family (esp. *Ambrosia* and *Artemisia*) (Scoggan, 1979). The plants have pink stems and purple flowers, and arise from the base of the host plant.

In the affected field in Nebraska, about 30% of sunflowers in 25% of the total area of the field were parasitized by *O. ludoviciana.* The parasitized plants were significantly stunted, with smaller heads and thinner stalks. It is uncertain if yields were impacted. This new finding has raised some concern for sunflower growers in the Great Plains region.

In Canada, sunflowers represent a small but important part of the Prairie agricultural industry. Approximately 35,000 ha of sunflowers are seeded each year, resulting in an annual production of about 67,000 tonnes of sunflower seeds (Statistics Canada, 2015). *Orobanche* species are regulated at the genus level under Canada's *Plant Protection* Act; however, *O. ludoviciana* is an exception because it is a native plant in Canada. Awareness of this plant and its potential to parasitize sunflowers may be important for early detection and management of infections should they occur.

SOURCES: Harveson, R. M., Nelson, A., Mathew, F. M. and Seiler, G. J. (2015) First report of *Orobanche ludoviciana* parasitizing sunflowers. Plant Health Progress doi:10.1094/PHP-B R-15-0043.

Scoggan, H. J. (1979) Flora of Canada. National Museums of Canada, Ottawa.

Statistics Canada. (2015) Tables by subject: Crops and horticulture. Field and special crops. [Online] Available: http://www.statcan.gc.ca/tables- tableaux/sum-som/l01/ind01/l3_920_2024-eng.ht m?hili_prim11 [5 Jan 2016].

7 Pathway: Proposed changes to ballast water management – implications for invasive plants and plant pests

Ballast water has long been recognized as a significant vector for the transport and introduction of new invasive species both in Canada and around the world. Ballast is taken on board ships to control their stability and trim, but because it is typically taken up and released in different locations it can facilitate the rapid movement of species, sometimes over large distances. Ballast water is attributed with introducing a number of harmful invasive species in Canada, including zebra mussels, quagga mussels, round goby and spiny water flea in the Great Lakes Region, and others such as the green crab and common periwinkle in coastal areas. Ballast water and associated sediment can also be a vector for aquatic and wetland plants, and associated pests

and diseases.

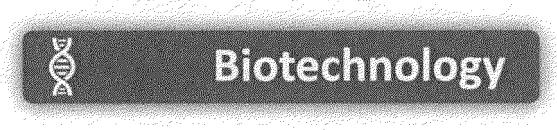
In Canada, ballast water management (BWM) guidelines have been in place since the 1980s, and statutory regulations under the *Canada Shipping Act* have been in effect since 2006. Current regulations apply to all Canadian vessels worldwide, as well as non-Canadian vessels operating in waters under Canadian jurisdiction. They require ballast water to be treated, exchanged, transferred to a reception facility or retained on board, to minimize the possibility of spreading harmful organisms. By far the most common management method used in Canada and around the world is mid-ocean exchange (MOE), which works on the principle of differences in water conditions (primarily salinity) between source and exchange locations. For example, many ships take up and release ballast in freshwater ports, crossing the ocean in between. Exchanging the ballast mid-ocean exposes freshwater organisms to intolerable salinity levels, and ensures that ballast exchange occurs between ecologically different zones, thus lowering the risk of invasion. However, there are a number of limitations to existing regulations and the practice of MOE, particularly for vessels moving and practicing MOE within or between marine systems where salinity levels are similar.

In 2010, Canada ratified the International Maritime Organization (IMO)'s *International Convention for the Control and Management of Ships' Ballast Water and Sediments* (BWMC). This was the first attempt at an international, legally binding legislation for BWM, and will come into effect twelve months after ratification by 30 member states representing at least 35% of the world shipping tonnage (currently at 43 states and 32.54%). The convention introduces new requirements for on-board testing and concentration-based discharge standards (the "D-2 standards"), although the effectiveness of a number of treatment systems certified under this program have been called into question. Currently, Transport Canada is deliberating how to proceed with implementation of the IMO D-2 standards, and the exact nature and timing of any new BWM requirements at the national level remains unclear. In the meantime, Transport Canada has initiated discussions with the CFIA about possible implications of these new requirements for the risk associated with plants and plant pests that could be transported in ballast water or associated sediment.

SOURCES: Cohen, A. N. and Dobbs, F. C. (2015) Failure of the public health testing program for ballast water treatment systems. Marine Pollution Bulletin 91(1): 29-34.

Mills, E. L., Leach, J. H., Carlton, J. T. and Secor, C. L. (1993) Exotic species in the Great Lakes: A history of biotic crises and anthropogenic introductions. Journal of Great Lakes Research 19(1): 1-54.

Scriven, D. R., DiBacco, C., Locke, A. and Therriault, T. W. (2015) Ballast water management in Canada: A historical perspective and implications for the future. Marine Policy 59: 121-133.



8 Review: The global outlook for genetically modified crops

The development and cultivation of genetically modified (GM) crops is increasing on a global scale. The global pipeline of GM crops is evolving, and this has implications for the international trade of agricultural commodities. In 2008, the European Commission's Joint Research Centre (JRC) examined the global situation of GM crops in development (Stein and Rodríguez-Cerezo, 2009). A follow-up document published in January 2016

(Parisi et al., 2016) reported that GM events nearly doubled from 2008 to 2015.

Diversity of GM crop types and traits are increasing at all stages of development. Crop types are currently dominated by maize, cotton, soybean and oilseed rape. However, biomass for liquid fuels and industrial products is becoming an important sub-sector of GM crops, driven by market demand. Rice and potatoes are also major upcoming GM crops, and cereals, fruits and vegetables are also under development in Brazil, India and China. Public developers in India and China are becoming increasingly active in GM crop development. New, smaller companies are emerging in the United States, India and other parts of Asia. Although herbicide-tolerance and insect-tolerance are the most dominant traits for GM crops, herbicide-tolerance traits are shifting from glyphosate and glufosinate to other active ingredients such as sulfonylurea, 2,4-D, dicamba, isoxaflutole and oxynil. New and emerging traits are being developed worldwide, particularly in Asia, including insect-resistant eggplant (India), insect-resistant poplar (China) and virus-resistant bean (Indonesia). Important traits in African countries include insect and disease tolerance, abiotic stress tolerance (i.e., drought) and biofortification for human nutrition in crops such as banana, cowpea and rice. The development of crops with more than one improved agronomic trait is becoming increasingly common. Known as 'stacked varieties', these may be developed using molecular tools or through conventional breeding of two or more plant lines with GM events. Stacked varieties are projected to play a major role in the development of upcoming GM crops. Unfortunately, there are large discrepancies in the regulatory treatment of stacked varieties across countries, which can result in asynchronous authorization.

In summary, the current trend towards increasing development and cultivation of GM crops in diverse geographic regions is projected to continue. Thus, there is a strong need for international dialogue to minimize the negative effects of asynchronous authorization on global agricultural trade.

SOURCES: Parisi, C., Tillie, P. and Rodríguez-Cerez o, E. (2016) The global pipeline of GM crops out to 2020. Nature Biotechnology 34(1): 31-36.

Stein, A.J. and Rodríguez-Cerezo, E. (2009) The global pipeline of new GM crops. Implications of asynchronous approval for international trade. European Commission, Joint Research Centre.

9 New Technology: The patent battle over CRISPR-Cas9 techniques

We often remark about the great potential of emerging technologies, but rarely do we observe them moving quickly from discovery to commercialization. CRISPR gene editing systems are certainly bucking this trend. Since 2012, when CRISPRs were first engineered to target specific genetic sequences *in vitro*, the technology has been used to successfully edit bacterial, fungal, animal and plant genomic sequences *in vivo*. Moreover, an intense foundational technology patent battle has emerged between scientists at the University of California, Berkley and the Broad Institute of MIT and Harvard. The outcome of this patent battle will influence hundreds of millions of dollars already committed to CRISPR-based companies.

The patent dispute traces back to March 15, 2013 when Jennifer Doudna and Emmanuelle Charpentier, of UC Berkley and the Max Plank Institute, respectively, filed for a joint CRISPR-Cas9 technique patent with the United States Patent and Trademark Office (USPTO). In October 2013, Feng Zhang of the Broad Institute of MIT filed to

protect his CRISPR-Cas9 technique using an expedited review. The Zhang patent was granted in April 2014, while the Doudna-Charpentier application was still being processed 2 years later. In January, 2016 the USPTO decided to review who should have been awarded the CRISPR-Cas9 patent; Doudna-Charpentier or Zhang. This process, called patent interference, functions much like a court case and will likely see both Doudna and Zhang deposed under oath with evidence used to establish what group invented the technique first. Many expect that laboratory notes will play a large part in establishing the timeline.

The outcome of these proceedings will be important for the agricultural biotechnology sector. Doudna's biotechnology start-up, Caribou Biosciences, recently announced a CRISPR-Cas9 patent sharing agreement with DuPont-Pioneer. Both groups possess CRISPR-Cas9 patents, and this partnership allows access to each other's CRISPR intellectual property. This partnership also divvies up the agricultural crop space; DuPont will develop crops like maize, soybean and canola, while Caribou Biosciences will be responsible for fruits and vegetables. If Doudna and Charpentier are unsuccessful in their interference challenge, then it's reasonable to expect that this Caribou Bioscience – DuPont partnership will have to restructure significantly, if it continues to exist at all.

For Canadian regulators, the outcome of this patent dispute may be interesting, but is unlikely to affect daily activities. Moreover, despite there being significant uncertainty over how CRISPR technologies will be treated by worldwide regulatory agencies, Canada's product based regulatory system is well positioned to address incoming Plants with Novel Traits derived from CRISPR-Cas9 tool sets.

SOURCES: Ledford, H. (2016) Bitter fight over CRISPR patent heats up. Nature 529, 265 doi:10.1038/nature.2015.17961.

Grushkin, D. (2016) DuPont in CRISPR-Cas patent land grab, Nature Biotechnology 34:1, 13 doi:10.1038/nbt0116-13.

Acknowledgments

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SCIENCE DES VÉGÉTAUX

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Contexte: La Direction des sciences de la protection des végétaux de l'Agence canadienne d'inspection des aliments (ACIA) effectue régulièrement un balayage des sources externes afin d'identifier toute information pouvant avoir de l'importance ou de l'intérêt, sur le plan réglementaire, pour le programme canadien de protection des végétaux. L'ACIA a rédigé le présent Survol - science des végétaux comme outil de sensibilisation, pour mettre en relief certaines questions d'intérêt et partager de nouvelles informations ayant de l'importance pour la protection des végétaux.

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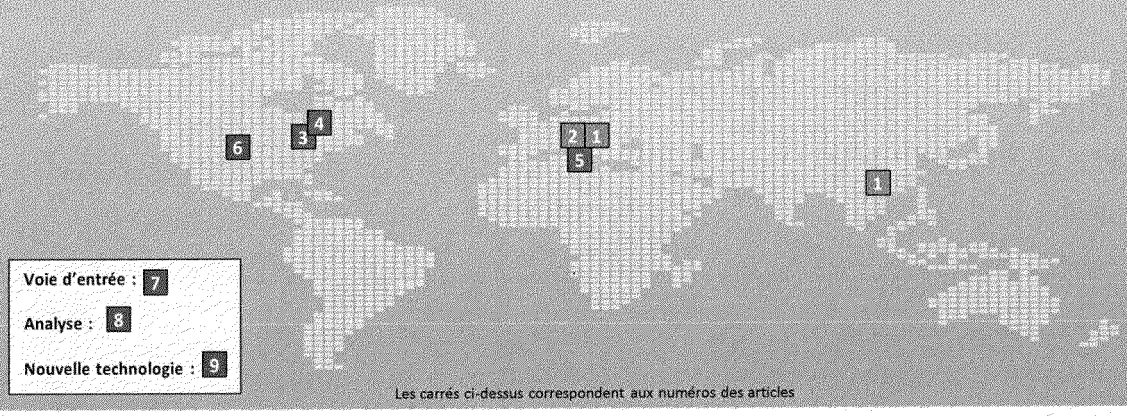

Les carrés ci-dessus correspondent aux numéros des articles

Agence canadienne d'inspection des aliments | Canadian Food Inspection Agency

Canada

Pathologie

1 Nouvel organisme nuisible : Détection d'un nouveau chancre attaquant le peuplier en Europe et en Asie

En 2009, une nouvelle maladie a été détectée chez des peupliers (*Populus x euramericana*) en Hongrie. Les principaux symptômes de la maladie sont la formation de fissures verticales dans l'écorce des sujets infectés et le suintement d'un exsudat brun collant à partir des chancres. Une bactérie a été isolée des exsudats et appelée *Lonsdalea quercina* subsp. *populi* (Tóth *et al*., 2013). Un article publié dans la revue *Plant Disease* indique que cette bactérie a également été isolée chez des *Populus x euramericana* en Chine. Les sujets infectés présentaient des chancres de l'écorce et des exsudats blancs spumeux; des sujets gravement infectés sont même morts (Li *et al*., 2014).

Une espèce étroitement apparentée, le *Lonsdalea quercina* subsp. *quercina*, a été identifiée comme l'agent causal d'une maladie appelée "drippy nut disease" chez le chêne aux États-Unis (Brady *et al*., 2012). Aucune mention pouvant laisser croire que l'une ou l'autre de ces deux bactéries pourrait être présente au Canada n'a été trouvée dans la littérature scientifique.

SOURCES : Brady C.L., Cleenwerck I., Denman S., Venter S.N., Rodríguez-Palenzuela P., Coutinho T.A. et De Vos P. (2012) Proposal to reclassify *Brenneria quercina* (Hildebrand & Schroth 1967) Hauben *et al*. 1999 into a novel genus, *Lonsdalea* gen. nov., as *Lonsdalea quercina* comb. nov., descriptions of *Lonsdalea quercina* subsp. *Quercina* comb. nov., *Lonsdalea quercina* subsp. *Iberica* subsp. nov., and *Lonsdalea quercina* subsp. *Britannica* subsp. nov., emendation of the description of the genus *Brenneria*, reclassification of *Dickeya dieffenbachiae* as *Dickeya dadantii* subsp. *Dieffenbachiae* comb. nov., and emendation of the description of *Dickeya dadantii*. International Journal of Systematic and Evolutionary Microbiology. 62: 1592–1602.

Li, Y., He, W., Ren, F., Guo, L., Chang, J., Cleenwerck, I. Ma, Y. et Wang, H. (2014) A Canker Disease of *Populus x euramericana* in China caused by *Lonsdalea quercina* subsp. *populi*. Plant Disease 98(3): 368-378 DOI 10.1094/PDIS-01-13-0115-RE.

Tóth, T., Lakatos, T. et Koltay, A. (2013) *Lonsdalea quercina* subsp. *populi* subsp. nov., isolated from bark canker of poplar trees. International Journal of Systematic and Evolutionary Microbiology 63: 2309-2313 DOI 10.1099/ijs.0.042911-0.

2 Mise à jour : Détection du '*Candidatus* Phytoplasma prunorum' (enroulement chlorotique de l'abricotier) dans des vergers d'abricotiers en République tchèque

Les auteurs d'une étude récente font le point sur le statut du '*Candidatus* Phytoplasma prunorum' (enroulement chlorotique de l'abricotier) en République tchèque, où la maladie a été décelée pour la première fois il y a plus de 15 ans. Les données de surveillance à long terme du '*Candidatus* Phytoplasma prunorum' dans les vergers démontrent que la maladie est une source de préoccupation croissante pour les producteurs. Un taux d'infection de 50 % et un taux de mortalité moyen de 30 % (jusqu'à 40 % chez les jeunes arbres) sont observés dans les vergers d'abricotiers, même dans ceux où des arbres certifiés sont plantés. Les symptômes de la maladie sont passablement variables, mais le symptôme le plus fréquemment observé chez les abricotiers durant cette étude était l'enroulement chlorotique des feuilles.

Le '*Candidatus* Phytoplasma prunorum' est reconnu comme présent dans la plupart des pays européens et inflige des pertes importantes dans les vergers d'abricotiers, de pêchers et de pruniers japonais. Il est considéré comme un organisme de quarantaine au Canada.

SOURCE : Nečas, T., Ondrásek, I. et Krska, B. (2015) 'Candidatus Phytoplasma prunorum' (European stone fruit yellow) - a pathogen spreading uncontrollably in apricot orchards in the Czech Republic. Acta Hortic 1105: 131-136 DOI: 10.17660/ActaHortic. 2015.1105.19.

Entomologie

3 Mise à jour : Frênes résistants à l'agrile du frêne

L'agrile du frêne (*Agrilus planipennis*) (Coleoptera: Buprestidae) est un organisme de quarantaine réglementé au Canada, mais il est pour l'instant présent uniquement dans certaines régions de l'Ontario et de l'est du Québec. Des mesures interdisant le déplacement de matériel de frêne et de bois de chauffage ont été mises en place pour freiner la propagation du ravageur et « gagner du temps » en attendant que les études sur la résistance des frênes au ravageur débouchent sur la mise au point de traitements susceptibles d'entraver davantage la dispersion du ravageur ou de préserver des arbres de grande valeur.

Villari *et al.* (2016) ont récemment passé en revue la littérature existante afin d'analyser les mécanismes sous-tendant la variation interspécifique et intraspécifique de la résistance des frênes à l'agrile du frêne. Au terme de cette revue de la littérature, les constats suivants s'imposent :

- Le frêne de Mandchourie était moins recherché par les adultes pour l'alimentation et la ponte que les espèces sensibles d'Amérique du Nord et résistait mieux à l'alimentation des larves (Chakraborty *et al.*, 2014; Rigsby *et al.*, 2014).

- Le stress causé par la sécheresse avait pour effet d'affaiblir la résistance du frêne de Mandchourie mais n'avait aucun effet sur les composés phénoliques corticaux constitutifs, ce qui donne à croire que ces composés ne contribuent pas à l'augmentation de la sensibilité observée en réaction au stress causé par la sécheresse (Chakraborty *et al.*, 2014).

- L'application de jasmonate de méthyle a été associée à une élévation des concentrations corticales de verbascoside, de lignine et/ou d'inhibiteurs de la trypsine, qui ont réduit la survie et/ou la croissance larvaire lors de bioessais; ces résultats donnent à croire que le frêne rouge, le frêne blanc et le frêne noir possèdent un potentiel de résistance qui ne s'exprime pas en présence de conditions naturelles (Whitehill *et al.*, 2014).

Les auteurs font état d'une découverte intrigante, celle d'une très petite proportion de frênes rouges qui ont survécu aux attaques de l'agrile du frêne dans des peuplements gravement infestés. Cette découverte donne à croire que ces « frênes persistants » pourraient constituer une source de matériel pour l'étude des caractères de résistance. Dans le cadre d'une étude récente, Koch *et al.* (2015) ont évalué la variation intraspécifique chez les « frênes persistants » susmentionnés dans le but de déterminer les caractères particuliers ou les phénotypes probablement associés à une capacité accrue à survivre à une infestation par l'agrile du frêne. Trois sélections ont été significativement moins attaquées par les agriles adultes cherchant à s'alimenter, mais aucun composé foliaire volatile particulier n'a été associé à cette réduction de préférence, et des différences significatives liées au développement larvaire ont été relevées chez deux sélections. Les résultats révèlent que plusieurs mécanismes sont vraisemblablement responsables de la résistance exprimée par certains frênes. Koch et al. (2015) recommandent de poursuivre la surveillance et de préserver les frênes qui satisfont aux critères des « frênes persistants » et qui pourraient mener à la découverte de nouvelles

sélections d'espèces de frênes nord-américaines résistantes à l'agrile du frêne et à l'identification des sources de gènes de résistance pour les programmes de sélection.

SOURCES: Chakraborty, S., Whitehill, J.G.A., Hill, A.L., Opiyo, S.O., Cipollini, D., Herms, D.A. et Bonello, P. (2014) Effects of water availability on emerald ash borer larval performance and phloem phenolics of Manchurian and black ash. Plant, Cell and Environment 37: 1009-1021.

Koch, J.L., Carey, D.W., Mason, M.E., Poland, T.M. et Knight, K.S. (2015) Intraspecific variation in *Fraxinus pennsylvanica* responses to emerald ash borer (*Agrilus planipennis*). New Forests 46: 995-1011.

Villari, C., Herms, D. A., Whitehill, J. G., Cipollini, D. et Bonello, P. (2016) Progress and gaps in understanding mechanisms of ash tree resistance to emerald ash borer, a model for wood-boring insects that kill angiosperms. New Phytologist 209: 63-79.

Whitehill, J.G.A., Rigsby, C.M. Cipollini, D., Herms, D.A. et Bonello, P. (2014) Decreased emergence of emerald ash borer from ash treated with methyl jasmonate is associated with induction of general defense traits and the toxic phenolic compound verbascoside. Oecologia 176: 1047-1059.

4 Nouvel organisme nuisible : L'*Agrilus ribesi*, présent mais non détecté en Amérique du Nord depuis un siècle

La présence en Amérique du Nord de l'espèce eurasienne *Agrilus ribesi* a été mentionnée pour la première fois par Jendek *et al*. (2015). Cette espèce est maintenant présumée responsable des dommages infligés aux gadelliers et groseilliers (*Ribes* spp.) en Ontario, antérieurement attribués à l'*A. cuprescens* (Garlick, 1940). Cette découverte origine de la mention par Garlick du gadellier noir (ou cassissier), du gadellier rouge et d'autres *Ribes* spp. comme plantes hôtes de l'*A. cuprescens* en Ontario, lesquelles ne figuraient pas parmi les espèces citées comme telles dans la liste plus récente des plantes hôtes vérifiées (Jendek, 2003; Jendek et Poláková, 2014). La biologie de l'*A. cuprescens,* ravageur notoire des *Rubus* spp. et *Rosa* spp., est bien documentée, mais le développement de l'espèce à partir de *Ribes* spp. n'a jamais été confirmé. Un examen critique de tous les spécimens d'*A. cuprescens* conservés dans la Collection nationale canadienne a révélé que 16 d'entre eux étaient en réalité des *A. ribesi*.

Dans l'article qu'ils ont publié récemment, Jendek *et al*. (2015) présentent des caractères morphologiques distinctifs pour les deux espèces d'*Agrilus* ainsi que les codes-barres d'ADN de quatre espèces d'*Agrilus* exotiques établies en Amérique du Nord (*A. ribesi, A. cuprescens, A. planipennis* et *A. sulcicollis*) permettant leur identification sur la base de leur ADN. La faible variabilité génétique observée chez les populations nord-américaines de l'*A. cuprescens* et de l'*A. ribesi* donne à croire que la présence de ces deux espèces en Amérique du Nord résulte dans chaque cas d'une introduction unique.

SOURCES : Garlick, W.G. (1940) Notes on the rose stem girdler, *Agrilus communis rubicola* Abeille. Canadian Entomologist. 72: 21-23.

Jendek, E. (2003) Revision of *Agrilus cuprescens* (Ménétriés, 1832) and related species (Coleoptera: Buprestidae). Zootaxa 317: 1-22.

Jendek, E., Grebennikov, V. et Bocak, L. (2015) Undetected for a century: Palaearctic *Agrilus ribesi* Schaefer (Coleoptera: Buprestidae) on currant in North America, with adult morphology, larval biology and DNA barcode. Zootaxa 4034(1): 112-126.

Jendek, E. et Poláková, J. (2014) Host plants of world *Agrilus* (Coleoptera: Buprestidae). A critical review. Springer, Berlin, 706 pp.

5 Nouvel hôte : Ajout des poivrons de serre à la liste des hôtes du *Bactra bactrana*, une enrouleuse associée aux Cypéracées

Dans un article récent, Roditakis *et al*. 2015 associent pour la première fois le *Bactra bactrana* (Lepidotpera: Tortricidae) au poivron (*Capsicum annuum*) sur la base d'une infestation détectée dans deux serres dans le sud de la Crète, en Grèce. Les symptômes associés à l'alimentation larvaire des chenilles rappelaient les dommages infligés par des espèces qui se nourrissent à l'intérieur des

fruits et comprenaient de petites perforations pratiquées à la surface des poivrons et des dommages internes. Étant donné l'ampleur des taux d'infestation des fruits observés dans les deux serres (30 % et 15 %), le *B. bactrana* peut être considéré comme un ravageur potentiel du poivron. Les facteurs à l'origine de ce changement d'hôte important sont inconnus, car le *B. bactrana* est présent dans d'autres régions de l'Europe produisant des poivrons sans y causer de dommage.

D'autres espèces appartenant à ce genre ont été utilisées pour la lutte contre des mauvaises herbes. La présente découverte rappelle la nécessité d'évaluer de façon approfondie la gamme d'hôtes des organismes pressentis à titre d'agents de lutte biologique avant de procéder à leur lâcher dans leur contrée d'adoption. Bien que certaines associations soient imprévisibles, il importe d'inclure dans ces essais les plantes d'hôtes présentant une importance économique certaine, même si la gamme d'hôtes connue de l'agent de lutte biologique considéré est étroite.

SOURCE : Roditakis, E., Morin, S. et Baixeras, J. (2015) Is *Bactra bactrana* (Kennel, 1901) a novel pest of sweet peppers? Bulletin of Entomological Research 1-7 DOI:10.1017/S00074853150 00917.

Botanique

6 Première mention : Détection d'une espèce parasite du genre *Orobanche* dans un champ commercial de tournesol aux États-Unis

En septembre 2014, la plante parasite des racines *Orobanche ludoviciana* a été découverte dans un champ commercial de tournesol, dans le comté de Kimball, dans le Nebraska. Cette mention représente le premier cas jamais signalé dans l'hémisphère occidental de parasitisme d'une production commerciale de tournesol par une espèce du genre *Orobanche*.

Les espèces du genre *Orobanche* sont des plantes parasites obligatoires qui établissent des connexions vasculaires avec les racines de leurs plantes hôtes et obtiennent ainsi les éléments nutritifs et l'eau dont ils ont besoin. L'*O. cumana* est un parasite dévastateur du tournesol bien connu et largement répandu en Europe. Pour sa part, l'*O. ludoviciana* est indigène en Amérique du Nord et largement réparti dans la région des Grandes Plaines. Au Canada, il se rencontre dans le sud de la Colombie-Britannique et des provinces des Prairies et est un parasite reconnu d'autres membres de la famille des Astéracées (en particulier des genres *Ambrosia* et *Artemisia*) (Scoggan, 1979). La plante, reconnaissable à ses tiges roses et à ses fleurs violettes, se dresse à partir de la base de sa plante hôte.

Dans le champ infesté, au Nebraska, environ 30 % des tournesols, répartis sur 25 % de la superficie totale du champ, étaient parasités par l'*O. ludoviciana*. Les sujets parasités étaient significativement plus petits et présentaient des capitules plus petits et des tiges plus fines que les sujets sains. Bien qu'on ignore si le parasite a eu un impact sur les rendements, cette découverte suscite des inquiétudes chez les producteurs de tournesol de la région des Grandes Plaines.

Le tournesol représente une part modeste mais néanmoins importante de la production agricole des Prairies canadiennes. Environ 35 000 ha sont affectés chaque année à la culture du tournesol, pour une production annuelle d'environ

67 000 tonnes de graines de tournesol (Statistique Canada, 2015). Les espèces du genre *Orobanche* sont réglementées au niveau générique en vertu de la *Loi sur la protection des végétaux* du Canada, mais l'*O. ludoviciana* fait exception parce qu'il s'agit d'une plante indigène au Canada. La détection précoce et, le cas échéant, la mise en place de mesures de lutte reposent sur une meilleure connaissance de cette espèce nuisible et de sa capacité de parasiter les cultures de tournesol.

SOURCES: Harveson, R. M., Nelson, A., Mathew, F. M. et Seiler, G. J. (2015) First report of *Orobanche ludoviciana* parasitizing sunflowers. Plant Health Progress doi:10.1094/PHP-B R-15-0043.

Scoggan, H. J. (1979) Flora of Canada. National Museums of Canada, Ottawa.

Statistics Canada. (2015) Tables by subject: Crops and horticulture. Field and special crops (en ligne). Disponible à l'adresse : http://www.statcan.gc.ca/tables- tableaux/sum-som/l01/ind01/l3_920_2024-eng.ht m?hili_prim11 (consulté le 5 janvier 2016) (Également disponible en français : Statistique Canada. (2015) Tableaux par sujet : Cultures et horticulture. Grandes cultures et cultures spéciales. Disponible à l'adresse : http://www.statcan.gc.ca/tables- tableaux/sum-som/l02/ind01/l3_920_2024-fra.ht m?hili_none).

7 Voie d'entrée : Incidence des changements proposés à la gestion de l'eau de ballast sur la propagation de plantes et de phytoravageurs envahissants

L'eau de ballast est depuis longtemps reconnue comme un important vecteur de transport et d'introduction de nouvelles espèces envahissantes au Canada et ailleurs dans le monde. L'eau de ballast permet de gérer la stabilité et l'assiette des navires, mais comme son prélèvement et son rejet ont lieu à des endroits différents, elle peut faciliter le déplacement rapide d'espèces, parfois sur de grandes distances. L'eau de ballast est à l'origine de l'introduction au Canada d'un certain nombre d'espèces envahissantes nuisibles telles que la moule zébrée, la moule quagga, le gobie à taches noires et le cladocère épineux dans la région des Grands Lacs, ainsi que le crabe vert et le bigorneau dans les eaux côtières. L'eau de ballast et les sédiments peuvent également être vecteurs de plantes aquatiques et de plantes de milieux humides et des ravageurs et pathogènes qui leur sont associés.

Au Canada, des lignes directrices sur la gestion des eaux de ballast sont en place depuis les années 1980, et des règlements pris en application de la *Loi sur la marine marchande du Canada* sont en vigueur depuis 2006. La réglementation actuelle s'applique à tous les bâtiments canadiens où qu'ils soient, ainsi qu'aux bâtiments non canadiens naviguant dans les eaux de compétence canadienne. En vertu de cette réglementation, l'eau de ballast doit être traitée, renouvelée ou transbordée dans une installation de réception de l'eau de ballast ou conservée à bord des bâtiments, de manière à réduire au minimum la propagation d'organismes nuisibles. Le renouvellement de l'eau de ballast en pleine mer est de loin la méthode de gestion la plus couramment utilisée au Canada et ailleurs dans le monde. Cette méthode mise sur les différences liées aux conditions de l'eau (principalement la salinité) entre les points de ballastage et de déballastage. Par exemple, de nombreux bâtiments prélèvent et rejettent leur eau de ballast dans des ports situés en eau douce séparés par des zones de haute mer. Le renouvellement de l'eau de ballast en pleine mer expose les organismes d'eau douce à des concentrations de sel intolérables et réduit le risque d'invasion du fait qu'il se déroule dans des zones écologiquement différentes. Toutefois, la réglementation en vigueur et la pratique du renouvellement en pleine mer comportent certaines limites, en particulier dans le cas des bâtiments qui naviguent et renouvellent leur eau

de ballast dans des systèmes marins présentant des niveaux de salinité similaires.

En 2010, le Canada a ratifié la *Convention internationale pour le contrôle et la gestion des eaux de ballast et sédiments des navires de l'Organisation maritime internationale* (OMI). Il s'agissait de la première tentative de mettre en place une loi internationale ayant force exécutoire sur la gestion de l'eau de ballast. La Convention entrera en vigueur douze mois suivant sa ratification par 30 États membres représentant au moins 35 % du tonnage marchand mondial (43 États représentant 32,54 % du tonnage ont actuellement ratifié la Convention). La Convention impose de nouvelles exigences relativement aux analyses qui doivent être effectuées à bord des navires et aux normes fondées sur les concentrations applicables aux rejets (« règle D-2 »), bien que l'efficacité d'un certain nombre de systèmes de traitement certifiés en vertu de ce programme ait été mise en cause. À l'heure actuelle, Transports Canada s'interroge sur la façon d'appliquer la règle D-2 de l'OMI, et la nature exacte et la date de l'entrée en vigueur des éventuelles nouvelles exigences applicables à la gestion de l'eau à l'échelle nationale demeurent à préciser. Entre-temps, Transport Canada a amorcé des discussions avec l'ACIA concernant les répercussions possibles de ces nouvelles exigences sur les risques associés aux plantes et aux organismes nuisibles attaquant les végétaux qui pourraient être transportés dans l'eau de ballast ou les sédiments qui y sont associés.

SOURCES : Cohen, A. N. et Dobbs, F. C. (2015) Failure of the public health testing program for ballast water treatment systems. Marine Pollution Bulletin 91(1): 29-34.

Mills, E. L., Leach, J. H., Carlton, J. T. et Secor, C. L. (1993) Exotic species in the Great Lakes: A history of biotic crises and anthropogenic introductions. Journal of Great Lakes Research 19(1): 1-54.

Scriven, D. R., DiBacco, C., Locke, A. & Therriault, T. W. (2015) Ballast water management in Canada: A historical perspective and implications for the future. Marine Policy 59: 121-133.

Biotechnologie

8 Analyse : Perspectives mondiales pour les cultures des plantes génétiquement modifiées

Le développement et la culture de plantes génétiquement modifiées (GM) s'intensifient à l'échelle mondiale. La gamme de cultures GM est en pleine expansion à l'échelle mondiale, et ces changements ont une incidence sur le commerce international des produits agricoles. En 2008, le Centre commun de recherche (JRC) de la Commission européenne a procédé à un examen de la situation mondiale des cultures GM en développement (Stein et Rodríguez-Cerezo, 2009). Un document de suivi publié en janvier 2016 révèle que le nombre de produits GM a pratiquement doublé de 2008 à 2015 (Parisi *et al.*, 2016).

La diversité des types de cultures et des caractères GM est en hausse à toutes les étapes de développement. Les types de cultures sont actuellement dominés par le maïs, le coton, le soja et le colza oléagineux. Toutefois, sous l'impulsion de la demande du marché, la production de combustibles liquides à partir de la biomasse et de produits industriels est en voie de devenir un sous-secteur important des cultures GM. Le riz et la pomme de terre sont également des cultures GM en plein essor, et les céréales, les fruits et les légumes sont également l'objet de travaux de développement au Brésil, en Inde et en Chine. En Inde et en Chine, le secteur public joue un rôle de plus en plus important dans le développement des

cultures GM. De nouvelles entreprises de taille plus modeste émergent aux États-Unis, en Inde et dans d'autres régions de l'Asie. Même si la tolérance aux herbicides et aux insectes sont les caractères les plus dominants pour les cultures GM, on observe, dans le cas des caractères de tolérance aux herbicides, une transition du glyphosate et du glufosinate à d'autres matières actives telles que les sulfonylurées, le 2,4-D, dicamba, l'isoxaflutole et l'oxynil. Des caractères nouveaux et émergents sont développés partout dans le monde, en particulier en Asie, où l'on a mis au point une variété d'aubergine résistante aux insectes (Inde), une variété de peuplier résistante aux insectes (Chine) et une variété de haricot résistante aux virus (Indonésie). En Afrique, des efforts considérables sont investis dans le développement de nouvelles variétés présentant une tolérance aux insectes et aux maladies ou aux stress abiotiques (p. ex. sécheresse) et dans la biofortification de cultures destinées à la consommation humaine telles que les bananes, le dolique et le riz. La mise au point de plantes cultivées possédant plus d'une caractéristique agronomique améliorée est de plus en plus fréquente. La mise au point de telles plantes appelées « variétés à gènes empilés » peut se faire à l'aide d'outils moléculaires ou de méthodes de sélection classiques prévoyant le croisement d'au moins deux lignées végétales GM. On s'attend à ce que les variétés à gènes empilés jouent un rôle majeur dans le développement futur de nouvelles cultures GM. Malheureusement, le traitement réglementaire réservé aux variétés à gènes empilés diffère considérablement d'un pays à l'autre, et ces divergences peuvent mener à des autorisations asynchrones.

En bref, l'intensification générale actuelle du développement et de la production de cultures GM dans diverses régions du monde est appelée à se poursuivre. Il est donc très important de maintenir un dialogue international afin de réduire le plus possible les effets négatifs des autorisations asynchrones sur le commerce mondial des produits agricoles.

SOURCES : Parisi, C., Tillie, P. et Rodriguez-Cerezo , E. (2016) The global pipeline of GM crops out to 2020. Nature Biotechnology 34(1): 31-36.

Stein, A.J. et Rodríguez-Cerezo, E. (2009) The global pipeline of new GM crops. Implications of asynchronous approval for international trade. European Commission, Joint Research Centre.

9 Nouvelle technologie : Contentieux de brevets portant sur la méthode CRISPR-Cas9

Nous faisons souvent allusion au grand potentiel des technologies émergentes, mais nous assistons rarement au passage rapide de ces technologies de la découverte à la commercialisation. Le système de manipulation génétique CRISPR va certainement à l'encontre de cette tendance. Destinée à l'origine à être utilisée pour modifier des séquences génétiques spécifiques *in vitro*, la méthode CRISPR a été utilisée avec succès depuis 2012 pour modifier des séquences génomiques *in vivo* de bactéries, de champignons, d'animaux et de végétaux. Une intense guerre de brevets portant sur cette technologie de base oppose maintenant des scientifiques de l'University of California, Berkley et du Broad Institute of MIT and Harvard. L'issue de ce litige aura une incidence sur les centaines de millions de dollars déjà investis par les entreprises engagées dans la mise au point de cette technologie.

Le conflit remonte au 15 mars 2013, alors que Jennifer Doudna et Emmanuelle Charpentier, respectivement de l'UC Berkley et du Max Plank Institute, ont déposé conjointement une demande de brevet pour la méthode CRISPR-Cas9 à l'United

States Patent and Trademark Office (USPTO). En octobre 2013, Feng Zhang, du Broad Institute of MIT, a déposé une demande de brevet pour protéger sa méthode CRISPR-Cas9 selon une procédure d'examen accéléré. Un brevet lui a été accordé en avril 2014, mais la demande de Doudna-Charpentier était toujours à l'examen deux ans plus tard. En janvier 2016, l'USPTO a décidé de revoir qui de Doudna-Charpentier ou de Zhang aurait dû se voir accorder le brevet pour la méthode CRISPR-Cas9. Cette procédure d'interférence, appelée revendication de priorité, fonctionne dans une large mesure comme une action en justice. Doudna et Zhang seront appelés à déposer sous serment, et les preuves recueillies seront utilisées pour déterminer quel groupe a inventé la technique en premier. Nombreux sont ceux qui croient que les notes de laboratoire joueront un grand rôle dans l'établissement de l'échéancier.

L'issue de ces procédures revêt une grande importance pour le secteur de la biotechnologie agricole. La société de biotechnologie de démarrage de Doudna, Caribou Biosciences, a récemment annoncé qu'elle avait conclu une entente de partage de brevets visant la technologie CRISPR-Cas9 avec DuPont-Pioneer. Les deux groupes possèdent des brevets pour cette technologie, et ce partenariat permettra à chacun d'avoir accès aux droits de propriété intellectuelle de l'autre liés à la technologie CRISPR. Ce partenariat leur permettra également de se répartir l'espace agricole, DuPont se spécialisant dans la mise au point de cultures telles que le maïs, le soya et le canola, et Caribou Biosciences, dans le développement de fruits et légumes. Si Doudna et Charpentier échouent dans leur procédure d'interférence, on peut raisonnablement s'attendre à une importante restructuration du partenariat Caribou Biosciences – DuPont, si tant est que sa viabilité n'est pas compromise.
Pour les organismes de réglementation canadiens, l'issue de ce contentieux de brevet peut être intéressante, mais elle n'aura vraisemblablement pas d'incidence sur les activités quotidiennes. En outre, en dépit des incertitudes importantes associées au traitement qui sera réservé aux technologies CRISPR par les organismes de réglementation du monde entier, le Canada, du fait que son système de réglementation est fondé sur les produits, est en bonne position pour examiner les végétaux à caractères nouveaux issus de la technologie CRISPR-Cas9.

SOURCES : Ledford, H. (2016) Bitter fight over CRISPR patent heats up. Nature 529, 265 doi:10.1038/nature.2015.17961.

Grushkin, D. (2016) DuPont in CRISPR-Cas patent land grab, Nature Biotechnology 34:1, 13 doi:10.1038/nbt0116-13.

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Merci aux employés suivants de l'ACIA qui ont contribué à cette édition de Survol - science des végétaux : K. Castro, J. Dalton, M. Damus, B. Day, J.-F. Dubuc, V. Grebennikov, D. Holden, W. Laviolette, D. Levac, A. Sissons, C. Wilson et L. Vyvey.

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From: Andrea Sissons
To: Wood, Michael
CC: Kapitan, Krista; Kuzyk, Tara; Schnell, Jaimie
Date: 2016-05-11 9:41 AM
Subject: Re: Fwd: PRAs required
Attachments: State of the Worlds Plants report 2016_0.pdf

Hey Mike,

Sadly this is a huge gap for us - I have included the link to the Invasive Alien Species strategy for Canada which does have some older data on impacts
http://www.collectionscanada.gc.ca/webarchives/20071116034707/http://www.cbin.ec.gc.ca/issues/ias.cfm?lang=e
As for the IRMF work - all we did was base the economic impact on the value of the commodity minus some percentage that we made up as an impact from a generic pest - no specific pest or numbers were used, it was very very generic, and not at all a solid case study!

This may be of interest
http://download.springer.com/static/pdf/137/art%253A10.1007%252Fs10530-011-9951-8.pdf?originUrl=http%3A%2F%2Flink.springer.com%2Farticle%2F10.1007%2Fs10530-011-9951-8&token2=exp=1462974186~acl=%2Fstatic%2Fpdf%2F137%2Fart%25253A10.1007%25252Fs10530-011-9951-8.pdf%3ForiginUrl%3Dhttp%253A%252F%252Flink.springer.com%252Farticle%252F10.1007%252Fs10530-011-9951-8*~hmac=494c06122e9ad6d39f34dcb52395ceef9d5dd6ed3cd472d8481a50fcaeebd55e

and also an excellent report on the State of the World's plants is attached

>>> Michael Wood 2016-05-10 2:51 PM >>>
Andrea
Pursuant to the email below, which I have sent on to Martin and France, do you have access to good economic risk data from the IRMF? Darlene Blair suggested you might and we are looking for some solid case studies for the ECONOMIC impact of pests in Canada or other jurisdictions. Any assistance you can provide would be much appreciated and feel free to canvas your groups as necessary or you see fit.

I would also introduce, by way of this email, Krista Kapitan, our student. She is studying environmental economics and will be working up some of these case studies with input and guidance from Jaimie, Tara and myself,

Mike

>>> Michael Wood 2016-05-10 2:48 PM >>>

>>> Michael Wood 2016-05-10 2:44 PM >>>
Rob
Can we get copies of the PRAs for Khapra beetle and Karnal Bunt? We are working up case studies for serious pests and Kanwal has suggested these. Krista, our student, has started a web search and put together some data, but we want more on the Canadian impacts.

Jason if you are aware of any documents or analysis for this, particularly economic analysis, we would be pleased to have it as well.

This material will be used t support ministers' conversations in July

As an aside, are we planning to do any work to update our PRAs for karnal bunt based on climate change?
Thanks
Mike

From: Sarah G. Davis
To: Biotech Team; Duff, Cameron; Macdonald, Janet E.; Schnell, Jaimie; T...
Date: 2016-05-12 4:15 PM
Subject: Fwd: Article in Nature Biotech on a risk-based approach to the regulation of GE organisms
Attachments: nbt.3568[1].pdf

An interesting article recently published in Nature Biotechnology is attached. Note that our insertional effects paper is cited!

S.

>>> "Kierstead, Kyle" <Kyle.Kierstead@AGR.GC.CA> 2016-05-12 12:58 PM >>>

FYI – the attached article recently published in *Nature Biotechnology* may be of interest given the recent work going on at the CFIA on retransformations and remutations. It focuses on U.S. regulations and talks about changes that APHIS is currently considering (and seeking input on). An expert is below:

GE plants are marked by an intended change—such as the introduction of herbicide tolerance or virus resistance—that is specifically tested for safety. Most GE events produce a protein or other metabolite(s) that can be tested for allergenicity and toxicity[42] (http://www.nature.com/nbt/journal/v34/n5/full/nbt.3568.html#ref42), [43] (http://www.nature.com/nbt/journal/v34/n5/full/nbt.3568.html#ref43). *These methods are well established and widely accepted and will not be covered here.*

Regulatory scrutiny is applied to individual 'transformation events' even when the same gene introduction has been evaluated many times previously, on the premise that the physical insertion of DNA into a genome could itself have hazardous, unintended effects by interfering with the normal functioning of endogenous genes[44] (http://www.nature.com/nbt/journal/v34/n5/full/nbt.3568.html#ref44). *The data indicate that such unintended changes are largely trait independent.*

Consequently, each time a given gene is introduced into a plant, regulators consider that a new 'event' is created—even when copies of a single construct are inserted multiple times into different plants of the same species. Just as conventional breeders will often test thousands of genetic variants in the field to select the best individual plants for commercial development, it is necessary to produce hundreds, if not thousands, of unique events in the lab to obtain a single event or a small number of events that are further developed for commercial introduction (the 'lead event')[45] (http://www.nature.com/nbt/journal/v34/n5/full/nbt.3568.html#ref45), [46] (http://www.nature.com/nbt/journal/v34/n5/full/nbt.3568.html#ref46). *But because each such event constitutes a unique product for the purposes of regulation, the field testing and marketing of any one of them requires the preparation of a unique data dossier and individual regulatory approval.*

The case for retiring such regulatory requirements has been strengthened by experience. A review by Weber et al.[47] (http://www.nature.com/nbt/journal/v34/n5/full/nbt.3568.html#ref47) *concluded that unintended DNA-level changes that could occur from GE are no different from those that occur in plant genomes naturally, a finding that was later substantiated in a review by Schnell et al.*[13] (http://www.nature.com/nbt/journal/v34/n5/full/nbt.3568.html#ref13). *Likewise, Steiner et al.*[26] (http://www.nature.com/nbt/journal/v34/n5/full/nbt.3568.html#ref26) *observed that novel toxins not known to occur at the genus level have never been known to arise spontaneously during conventional breeding. These findings are consistent with the prediction of the 1989 National Research Council analysis: "Crops modified by molecular and cellular methods should pose risks no different from those modified by classical genetic methods for similar traits. Because the molecular methods are more specific, users of these methods will be more certain about the traits they introduce into the plants."*

Of the many hundreds of thousands of plant varieties genetically improved with classic (pre-molecular) techniques that have been field tested, only a minuscule number (two, possibly three) have ever manifested any notable hazards for the environment, human health, or food safety. These exceptions listed by Steiner et al.[26] (http://www.nature.com/nbt/journal/v34/n5/full/nbt.3568.html#ref26) *all involved toxins already known to be in the crop, not unknown toxins appearing de novo, and thus were predictable. Furthermore, the injuries*

resulting from these crops were minor ones, such as stomach aches or skin rashes. It must be emphasized that all were the result of conventional breeding, not modification by recombinant DNA technology or genome-editing techniques. That is why new varieties of plants that are known to harbor relatively high levels of toxins, such as potato, are customarily analyzed to ensure that levels of potentially harmful substances remain in the safe range, regardless of the technique used to modify them. (Many foods, including licorice and nutmeg, normally contain substances that can be toxic at high levels but are perfectly safe in the amounts routinely consumed. Others, such as kidney beans and cassava, contain harmful levels of toxins that are denatured by proper preparation and cooking.)
Changing the focus from conventional breeding to molecular breeding, the Commonwealth Scientific and Industrial Research Organization (CSIRO) of Australia developed a transgenic pea in 2006 that raised concerns about increased allergenicity. But this 2006 event occurred from the intended change (for which the breeders properly tested and withdrew the pea) and was not an unintended effect of the inserted genetic material[48] (http://www.nature.com/nbt/journal/v34/n5/full/nbt.3568.html#ref48). Thus, even this 2006 CSIRO experience does not validate event regulation for unintended insertional effects, and a subsequent study indicates that withdrawing the transgenic pea may have been unnecessary anyway[49] (http://www.nature.com/nbt/journal/v34/n5/full/nbt.3568.html#ref49).

As in other forms of plant breeding, developers of recombinant DNA-modified plants typically screen hundreds or thousands of plants to identify candidates with the most desirable phenotypes[45] (http://www.nature.com/nbt/journal/v34/n5/full/nbt.3568.html#ref45). As Bradford et al.[50] (http://www.nature.com/nbt/journal/v34/n5/full/nbt.3568.html#ref50) observe, "Conventional breeding programs generally evaluate populations with much wider ranges of phenotypic variation than is observed in transgenic programs." Therefore, no scientific justification exists for event-specific regulation of crops modified with recombinant DNA or gene-editing technology.

USDA regulators implicitly recognize the fact that event-specific regulation is generally unwarranted, as demonstrated by their 'extension' process, an expedited regulatory mechanism that can extend deregulation decisions to 'similar' crops. However, as of 31 July 2015, the USDA had used the extension process just 18 times out of the 116 Determinations of Nonregulated Status currently listed on its web site[51] (http://www.nature.com/nbt/journal/v34/n5/full/nbt.3568.html#ref51). Only three of these had occurred since 2006, in part because companies petitioning for non-regulated status need to comply with regulatory requirements in foreign markets, which usually require full prior approval in the country of origin.

In the 24 years since the USDA's first deregulation of a GE crop, a vast amount of information on certain traits in certain crops has accumulated, and it is well established that there are no plant pest or noxious weed risks associated with already approved crop–gene combinations. Therefore, it is encouraging that the USDA recently announced it is reviewing its process for extending approvals[52] (http://www.nature.com/nbt/journal/v34/n5/full/nbt.3568.html#ref52). This APHIS review will allow a reduction in regulatory burdens by extending a deregulation decision from an already deregulated crop to a sufficiently similar crop. However, this APHIS modification represents a minimal, inadequate reduction in regulatory burdens for three reasons.

First, APHIS is not creating a categorical exemption for the sufficiently similar crop but rather using Section 340.6(e) of its existing regulations to lighten the review process for sufficiently similar crops.

Second, using existing authority, APHIS explicitly states that each extension of non-regulated status is a "major federal action" that triggers the requirements of the National Environmental Policy Act (NEPA).

And third, by giving guidance for a lesser regulatory review for the extension of an already granted deregulation decision, APHIS falls far short of the fundamental reforms needed (for example, a tiered risk analysis similar to that proposed in this article).
Regardless, APHIS decisions in recent years appear to some observers to have been driven not by the imperative to conduct science-based risk assessment as the basis for timely decisions on approvals, but by the need imposed by USDA Office of General Counsel (USDA-OGC) to prepare a paper trail to safeguard against abusive, harassing procedural lawsuits under NEPA. That GMO approvals are even subject to NEPA highlights another target area ripe for, and in dire need of, regulatory reform.

Cindy Pearson - RE: SAVE THE DATE: Health Portfolio Synthetic Biology Workshop *** Postponment Until the week of October 11-14 ***

From: "Atkinson, Andrew (HC/SC)" <andrew.atkinson@canada.ca>
To: "Tayabali, Azam (HC/SC)" <azam.tayabali@canada.ca>, "Arvanitakis, George...
Date: 2016-05-30 11:40 AM
Subject: RE: SAVE THE DATE: Health Portfolio Synthetic Biology Workshop *** Postponment Until the week of October 11-14 ***
CC: "Yambao, Kathrina (PHAC/ASPC)" <kathrina.yambao@phac-aspc.gc.ca>, "MarcS...

Dear all,

We've received feedback from participants, and it appears that June 15th conflicts with a number of previously scheduled meetings.

Given that we are running into summer months, we are postponing this event until the week of **October 11-14.**

Please let us know whether you'll likely have a conflict with that timing.

Take care all,

Andy

Andrew Atkinson
Manager, Emerging Sciences Policy / Gestionnaire, Politiques des sciences émergentes
Science Policy Directorate/Direction des politiques scientifiques
Strategic Policy Branch/Direction générale de la politique stratégique
Health Canada | Santé Canada
Phone: 613-948-8095
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Brooke Claxton Building | édifice Brooke Claxton, Room | pièce 967D
70, promenade Colombine Driveway, Pré Tunney's Pasture, Ottawa, Ontario K1A 0K9
Postal Locator | Indice postal : 0909C

From: Atkinson, Andrew (HC/SC)
Sent: 2016-05-20 4:17 PM
To: 'azam.tayabali@hc-sc.gc.ca'; 'george.arvanitakis@hc-sc.gc.ca'; 'deborah.ashby@hc-sc.gc.ca'; 'megan.bettle@hc-sc.gc.ca'; 'Phil.shwed@hc-sc.gc.ca'; 'Jason.Rancourt@hc-sc.gc.ca'; 'Souleh.semalulu@hc-sc.gc.ca'; 'karen.reynolds@hc-sc.gc.ca'; 'Genevieve.bondy@hc-sc.gc.ca'; 'Stephanie.hardy@hc-sc.gc.ca'; 'Anthony.ridgway@hc-sc.gc.ca'; 'david.lee@hc-sc.gc.ca'; 'Brian.belliveau@hc-sc.gc.ca'; 'titus.tao@hc-sc.gc.ca'; 'Brooke.walter@hc-sc.gc.ca'; 'Kirsten.jacobsen@phac-aspc.gc.ca'; 'philip.macdonald@inspection.gc.ca'; 'christine.tibelius@inspection.gc.ca'; 'dylan.levac@inspection.gc.ca'; 'Cindy.Pearson@inspection.gc.ca'; 'Ewa.Madey@inspection.gc.ca'; 'jflamenbaum@cihr-irsc.gc.ca'; 'briancolton@rogers.com'; 'rick.scroggins@canada.ca'; 'souad.elouakfaoui@canada.ca'; 'Neil.Macintosh@canada.ca'; 'Sabrina.Kim@canada.ca'; Griffiths, Jenna (HC/SC); Louter, Jim (EC/EC)

s.19(1)

Cc: Yambao, Kathrina (PHAC/ASPC); 'Marc Saner'
Subject: FW: SAVE THE DATE: Health Portfolio Synthetic Biology Workshop

Dear all,

This is a SAVE-THE-DATE notice for an upcoming Health Portfolio Synthetic Biology Workshop facilitated by Marc Saner:

Wednesday June 15, 2016, 09h00 - 16h00 (PHAC Media Room, 120 Colonnade Road).

An agenda and additional logistics will follow, as well as a calendar request.

Many of you have already been interviewed by Marc, who has been commissioned to identify potential regulatory or process gaps related to synthetic biology oversight throughout the Health Portfolio. The insights from the interviews will flow into a workshop backgrounder and a final report.

The workshop is an essential part of this process as it will allow us to collectively set priorities and - if there are any issues worthy of serious consideration - discuss ideas for solutions. We also wish to identify regulatory sectors not impacted by synthetic biology, regardless of novelty. This output will be used to better frame pressing issues for communication to senior management as well as assist with public communication.

Issues to be discussed may include risk analysis and regulations, human resources and expert capacity, communication and knowledge management, international issues and collaboration, etc.

In addition, we are considering opening the workshop with two external speakers:

- (Concordia University) will talk about Synthetic Biology, and its likely practical applications which will require regulatory oversight.
- We would also like to invite a representative from BioteCanada to briefly share thoughts on Synthetic Biology and regulatory issues they foresee.

and BioteCanada's role at this event will be specific; this is simply an opportunity for these speakers to briefly share their views, and answer questions we may for them. Once their talks are complete, the speakers will leave the meeting and the workshop will continue in-camera.

If you have any concerns about inviting these individuals or organizations, please contact me as soon as possible.

Regards

Andy

s.19(1)

From:
To: <jaimie.schnell@inspection.gc.ca>
Date: 2016-06-10 9:07 AM
Subject: Synthetic biology and gene editing in the healthcare & agriculture sectors

---
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)

Hi Jaimie

I am pleased to announce that the agenda for the third in our very successful Synthetic Biology meetings is now ready for publication. Click here (http://www.globalengage.co.uk/qpcr/agenda.html) to download the PDF of the agenda.

The meeting is co-located with the 4thqPCR& Digital PCR Congress (
http://www.globalengage.co.uk/qpcr.html?utm_source=ymlp&utm_medium=email&utm_term=Synthetic%20Biology&utm_content=Agenda%20&utm_campaign=Launch
) and the 2ndMicrofluidics Congress (

http://www.globalengage.co.uk/microfluidics.html?utm_source=ymlp&utm_medium=email&utm_term=Synthetic%20Biology&utm_content=Agenda%20&utm_campaign=Launch
) and your delegate pass gives you full access to all three meetings. However, in 2014 and 2015 we were forced to turn people away before the official closing date, as we simply had no more space. So I highly recommend early registration (http://www.globalengage.co.uk/synthetic/register.html?utm_source=ymlp&utm_medium=email&utm_term=Synthetic%20Biology&utm_content=Agenda%20&utm_campaign=Launch) which will also ensure you can take advantage of the 15% discount (using the early registration code NN/synbio/15) at www.globalengage.co.uk/synthetic/register.html.

The Synthetic Biology Congress will examine the latest developments in genome engineering, protein design, cell building, bio-manufacturing, gene editing as well as other technological developments affecting both the healthcare and plant biology sectors. New for 2016 the conference will also include a subsection focusing on synthetic engineering and the human microbiome, along with a stream examining advances in the tools and technologies that are fundamental to Synthetic Biology.

The rapid growth of the field is fuelled, in part, by the innovation and determination of younger members of the scientific community. As such there will be a number of talks by early career researchers, showcasing their ongoing work, allowing the audience to engage with some of the up-and coming names in the field.

The 2016 Agenda in Brief

Healthcare / Drug Discovery

* Academic &pharmaceutical synthetic biology case
* studies
* Genome engineering
* Synthetic Engineering and the Human Microbiome
* Applications of synthetic biology in health research
* Synthetic biology for exploiting and designing proteins

Plant Synthetic Biology

* Potential of synthetic biology in plant research
* Genome and pathway design / engineering
* Natural product biosynthesis
* Genome engineering / editing V CRISPR / TALENs etc.
* Plant research case studies
* Plant research for biofuels / bioproducts and pharmaceuticals

Technology and Tool Development

* Cell free expression
* High throughput microfluidics
* Computation tools and approaches
* Bio-manufacturing

* Bottom up approaches: cell building / genome assembly/building synthetic life

Read the full agenda here (http://www.globalengage.co.uk/synthetic/agenda.html?utm_source=ymlp&utm_medium=email&utm_term=Synthetic%20Biology&utm_content=Agenda%20&utm_campaign=Launch)

Confirmed Speakers

Jay Keasling, Professor of Chemical Engineering and Bioengineering, University of California, Berkeley, USA

Richard Kitney, Professor of Biomedical Systems Engineering, Imperial College London, UK

Karmella Haynes, Assistant Professor of Medical Engineering, Arizona State University, USA

Katherine Denby, Professor, School of Life Sciences, Warwick University, UK

Luis Rubio, Deputy Director, Centre for Plant Genomics and Biotechnology, Technical University of Madrid, Spain

Philippe Marliere, Scientific Director, Institute of Systems and Synthetic Biology, Genopole, Evry, France

Ines Ezcurra, Associate Professor, Plant Synthetic Biology Group, KTH Royal Institute of Technology, Sweden

Vincent Noireaux, Associate Professor, University of Minnesota, USA

Early Career Researcher Presentations

* Sequential bottom-up assembly of functional cell-like compartments
* Light-activated communication in Synthetic Tissues
* Design principles of transcription factor-based biosensors and high-throughput screening applications
* Expanding Nature's Catalytic Repertoire – Directed evolution of artificial membranes
* A RNA-based model based model-facilitated framework for designing generalizable genetic control systems
* Systematic characterisation of synthetic gene circuits using a high throughput microfluidic platform

See the full speaker panel (http://www.globalengage.co.uk/synthetic/speakers.html?utm_source=ymlp&utm_medium=email&utm_term=Synthetic%20Biology&utm_content=Agenda%20&utm_campaign=Launch)

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)

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)

If you have any questions, please feel free to contact me directly.

The 4th qPCR and Digital PCR Congress

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)

Microfluidics Newsletter (
http://www.globalengage.co.uk/microfluidics/newsletter.html?utm_source=ymlp&utm_medium=email&utm_term=Synthetic%20Biology&utm_content=Agenda%20&utm_campaign=Launch
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From: "Colton, Brian" <Brian.Colton@nrc-cnrc.gc.ca>
To: 'Kathrina Yambao' <kathrina.yambao@phac-aspc.gc.ca>, "andrew.atkinson@hc...
CC: Luc Bourbonniere <Luc.Bourbonniere@hc-sc.gc.ca>
Date: 2016-06-08 9:34 AM
Subject: McKinskey Offering on Syn Bio

I thought the group might be interested.

B.

http://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/exploring-the-disruptive-potential-of-synthetic-biology

From: CRISPR Application <CRISPR@genomeeditingtool.com>
To: <jaimie.schnell@inspection.gc.ca>
Date: 2016-07-04 10:49 AM
Subject: New CRISPR-Cas9 Stable Cell Lines

To view this email as a webpage, please click
http://www.genecopoeia.com/eflyers/us/?utm_source=GeneCopoeia&utm_medium=email&utm_campaign=Genome-Editing-20160615-NCBI-1&utm_unique=amFpbWllLnNjaG5lbGxAaW5zcGVjdGlvbi5nYy5jYQ%3D%3D%0A

s.19(1)

From: Philip Macdonald
To:
Date: 2014-04-03 5:17 PM
Subject: Publication in Transgenic Research

Hi

I noticed that and I wanted to feel out whether you thought your journal might be the right destination for us. A group of Canadian regulators have authored a paper that compares and contrasts the outcomes from conventional plant breeding techniques and those that arise from genetic engineering. The idea is to put the whole concept of insertional mutagenesis into context. Would this fit into your scope and if not would you have alternate suggestions? In the old days, we probably would have submitted to EBR.

Thanks for contributing to the AHTEG online forum. I always look forward to a post from you or I hope you will be submitting results from testing of the guidance.

Best regards,
Phil

Sarah G. Davis - Fwd: Re: PBO-PBRA retreat

From: Sarah G. Davis
To: de Graaff, Martine
Date: 2014-06-26 1:42 PM
Subject: Fwd: Re: PBO-PBRA retreat

Lots of ideas from Phil!

>>> Philip Macdonald 2014-06-26 12:46 PM >>>
Hi Sarah,

I will update on the AHTEG, the environmental consideration document, the new plant breeding technology workshop, Seed LLP and staffing changes in PBRA. I would also like the library cuts as an agenda item.

Phil

>>> Sarah G. Davis 2014-06-26 11:30 AM >>>
Hi Martine,

Those look like worthwhile topics! As for Michele - yes, the plan is for Michele to debrief a broader audience (including the PBO, AFD and HC) on the recent meeting she attended in Brussels on RNAi. It's been tricky trying to schedule this meeting, however, due to vacation conflicts. Perhaps we could add this topic to the PBO/PBRA retreat, given that it might be a little while before Michele has the chance to coordinate this broader meeting? I'm comfortable with this approach, so long as the PBO wouldn't mind potentially hearing some of the same messaging twice down the road? Phil, are you comfortable with this approach?

In terms of additional topics, perhaps PBRA could update on the status of biology documents? We've got quite a few at different stages of development. Phil, is there anything you'd like to include? Perhaps a debrief from the AHTEG meeting in Bonn?

I think you may have been working with Rhiannon on coordinating the retreat, however her last day with us is on Friday. Don't hesitate to let us know if there's a draft agenda in RDIMS that we can populate, or if we can help in any other way.

Cheers,
Sarah

>>> Martine de Graaff 2014-06-26 11:13 AM >>>
Hi Phil and Sarah,

I have a few topics we could address at our next retreat, including:

-Eddy's pipeline meeting in Spain
-NoS update on project development

There was talk of Michelle providing an update on the meeting she was recently at but HC did ask for a meeting on it, so would it be appropriate/possible for PBO to attend an info session with HC/Feed, when might this happen, and if PBO would be included in the session, would it be useful for her to provide an update at our retreat?

Any other issues we'd like to address?

thanks,
Martine

s.16(2)(c)

From: PlantResearchSeminar-SéminaireRechercheVégétaux
To: Plant Research Seminar/Séminaire recherche végéaux; PlantResearchSemina...
Date: 2015/01/21
Time: 1:00 PM - 2:00 PM
Subject: Plant Research Seminar Series/Séminaire de recherche en science des végéaux
Place: Webinar: Please view the poster for this seminar/Webinaire : Veuillez consulter l'affiche du séminaire
Attachments: Heather Shearer (seminar series).pdf; Heather Shearer (series de seminaries).pdf; CFIA_ACIA_-_#6236150_-_vR_-_Heather_Shearer_series_des_semina.DRF; CFIA_ACIA_-_#6236032_-_vR_-_Heather_Shearer_seminar_series014.DRF

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Plant Research & Strategies invites you to participate in this webinar.

Topic: **Targeted Gene-Editing Techniques: A New Horizon in Genome Customization**

Presented by: **Dr. Heather Shearer, Plant Biosafety Management Analyst, Canadian Food Inspection Agency**
Date: Wednesday, January 21, 2015
Time: 1:00 pm, Eastern Standard Time
Meeting Password:

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You can contact me at:
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s.16(2)(c)

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Sujet : **Techniques de modifications génétiques ciblées : Nouvel horizon dans la personnalisation du génome**
Présenté par : **Dr. Heather Shearer,** Analyste en gestion de la Biosécurité végétale, Agence canadienne d'inspection des aliments
Date : le mercredi 21 janvier 2015
Heure : 1:00 pm, Eastern Standard Time
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Targeted Gene-Editing Techniques: A New Horizon in Genome Customization

Presented by:
Dr. Heather Shearer
Plant Biosafety Management Analyst
Canadian Food Inspection Agency

Date: **January 21, 2015**
Time: **13:00-14:00 EST**

Live Location @
Health Canada's Banting Auditorium
251 Sir Frederick Banting Driveway

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Call-in toll-free number: 1-877-413-4788
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Abstract:
First, there was domestication, then, selective breeding. In the 20th century, we got inventive with atomic gardens, cloned animals, and crossed the species barrier using recombinant DNA techniques. The newest innovation in agricultural biotechnology has now arrived: targeted gene editing.
Gene editing techniques allow a genome to be precisely modified. Using customized engineered enzymes and synthesized nucleotide templates, it is now possible to "re-write" a specific gene sequence. For example, a single genetic locus controls whether cattle have horns. By editing only a few nucleotides in horned dairy cattle to be more like hornless beef cattle, a hornless trait could be introduced into the dairy breed, without changing any other breed characteristic. Beyond tweaking existing genes, gene editing techniques also allow the introduction of longer stretches of entirely new synthetic sequence, or can be used to excise a sequence from the genome. Genes can be moved from one chromosome to another, which simplifies conventional breeding by physically linking groups of desirable traits. "Landing pad" sites on a chromosome that allow optimal gene expression can be created and used to insert multiple new gene sequences at precise locations.
This presentation will provide basic details on the molecular biology of the CRISPR/Cas9, TALEN, and zinc-finger nuclease enzymes that make gene editing possible, and will discuss the kinds of genetic changes that can be envisioned.
With the rapid uptake and ease of use of these technologies, it is likely that products of gene editing will be submitted for pre-market assessment in the near future. For regulators, these techniques could pose some interesting challenges. Has something new been introduced if a genome has been rearranged? Is a novel trait present when a gene has been re-written to resemble another existing breed or variety? How does the use of a "landing pad" site relate to our understanding of recombinant DNA techniques, stacked products, and insertional effects? Are off-target mutations a concern, and how can they be detected? It is hoped that this presentation will spark further discussion of these and other science and policy questions relating to targeted gene editing.

For further information contact: amy.kehoe@inspection.gc.ca

Canada

Sarah G. Davis - Re: Fwd: Synthetic Biology - Topic 1: How to address the relationship between synthetic biology and biological diversity - A new message has been posted to the forum

From: Jaimie Schnell
To: Davis, Sarah G.; van der Lee, Nicole
Date: 2015-04-30 11:14 AM
Subject: Re: Fwd: Synthetic Biology - Topic 1: How to address the relationship between synthetic biology and biological diversity - A new message has been posted to the forum

It would be logical to do something under the Cartagena Protocol as opposed to something new, which would definitely mean we would lose some influence. There have been a number of interventions already to say that Syn Bio is captured under the definition of LMOs. I think if it is just agreed that Syn Bio is adequately addressed by the Cartagena Protocol, it would be business as usual.

Maybe we'll just end up seeing another annex to the Roadmap that sets out risk assessment for syn bio. That's probably more likely.

Jaimie

>>> Sarah G. Davis 2015-04-30 11:00 AM >>>
Interesting. Thanks for sharing, Jaimie. Do you worry that it could go in this direction? If I'm not mistaken, this would mean that Canada may lose some of its ability to influence the discussion?

>>> Jaimie Schnell 2015-04-30 7:33 AM >>>
is the first to call for the Cartagena Protocol to be expanded to encompass Syn Bio or for a new protocol to be written. If this is done, it is certainly something we would want to keep an eye on. Keep in mind that we are signatories to the Cartagena Protocol but have not ratified (i.e., we do not qualify as a Party, only as an observer), which is in contrast to the Convention on Biological Diversity (under which Syn Bio is currently being governed), which we have both signed and ratified, giving us full Party status.

Jaimie

>>> "bch@cbd.int" <bch@cbd.int> 2015-04-30 1:28 AM >>>

Dear Ms. Jaimie Schnell,

The following message has been posted by on **2015-04-30 00:21**.

RE: Opening of the discussion: "How to address the relationship between synthetic biology and biological diversity" *[#6858]*

This is my pleasure to participate in this forum. My name is I'm representing

Now days this early to talk on danger of synthetic biology impact to biodiversity. Specially for the development countries like
I have two proposals:
1. Research on synthetic biology should be supported to understand the nature of life, to develop new technologies to have sufficient products.
2. For the implementation of synthetic biology products regulation we should have strict regulation, expanding the Cartagena Protocol or establishing the new protocol on synthetic biology.

See this post in the online forum | Reply | Unsubscribe

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If you have any questions, suggestions or problems with the use of this service, please contact the Secretariat of the Convention on Biological Diversity at: bch@cbd.int

Sarah G. Davis - Fwd: RE: Presentations for the GLI - comments due April 27

From: Sarah G. Davis
To: Schnell, Jaimie; Tibelius, Christine
Date: 2015-05-04 1:14 PM
Subject: Fwd: RE: Presentations for the GLI - comments due April 27

FYI: The GLI meeting in Guadalajara was cancelled at the last minute!

>>> "Barnola, Luis" <Luis.Barnola@AGR.GC.CA> 2015-05-04 1:05 PM >>>
Same here Sarah—and I know how complex this LLP (in grain, and seed) file can be.
BTW, I believe you contributed to the preparations of the GLI meeting, which was supposed to be taking place as we speak in Guadalajara, Mexico. Unfortunately, the event was postponed at the last second last Friday due to violence that erupted precisely in the city where the meeting was expected to happen.

Yes, I remember that Phil's appointment was irreplaceable, so we would have lost the opportunity to keep working closely on this important file/venue.

If you need more background about our (AAFC/TTPD) involvement on the LLP in seed file please let me know.

LB

From: Sarah G. Davis [mailto:Sarah.Davis@inspection.gc.ca]
Sent: May-04-15 1:01 PM
To: Barnola, Luis
Subject: RE: Presentations for the GLI - comments due April 27

Hello Luis!

Yes, I remember when we worked together on SECs a while back. Coincidentally, I just sent you an email about LLP in seed without seeing this email first. I guess we're both interested in what the other person is up to!

With regards to your email below, Phil will continue his role as part of the AHTEG on risk assessment. Our thinking on this was that he as nominated as "Phil Macdonald" and not necessarily as the National Manager of the Plant and Biotechnology Risk Assessment Unit of the CFIA, and he has a long history with the file. Most of Phil's other responsibilities have been transitioned to me.

If you have any questions or wanted to connect on any other topic, please don't hesitate to let me know.

Sincerely,
Sarah

Sarah Davis, M.Sc.

A/National Manager, Plant and Biotechnology Risk Assessment Unit
Canadian Food Inspection Agency / Government of Canada
Sarah.Davis@inspection.gc.ca / Tel: 613-773-5271

Gestionnaire national par int., Unité d'évaluation des risques des végétaux et des produits de la biotechnologie
Agence canadienne d'inspection des aliments / Gouvernement du Canada
Sarah.Davis@inspection.gc.ca / Tél: 613-773-5271

www.inspection.gc.ca

>>> "Barnola, Luis" <Luis.Barnola@AGR.GC.CA> 2015-05-04 12:13 PM >>>
Hi Sarah,

How are you? I believe we met, long ago, when we participated with Phil in an online conference on socio-economic considerations as part of the Cartagena Protocol.

How is Phil doing? I heard that he's now Director and that you have taken (some of?) his files.

If that's true, are you also following up on Cartagena? (Particularly the Ad-Hoc Technical Expert Group on risk assessment and risk management)

As you probably know, this was one file that Phil and TTPD used to work closely together. Knowing that Phil has moved up I was curious to know what will happen with this (rather important) file.

Take care,
Luis Barnola

From: Sarah G. Davis [mailto:Sarah.Davis@inspection.gc.ca]
Sent: April-27-15 11:10 AM
To: Bergeron, Émilie; Tolusso, Giuliano; Goodwin, Jarett; Luc.Bourbonniere@hc-sc.gc.ca; Annie Savoie; Janet Lo; Michael Jay; Wendy Jahn; 'Jennifer.Fellows@international.gc.ca'(Jennifer.Fellows@international.gc.ca)
Cc: Barnola, Luis; Doré, Nathalie; Gauthier, Nicholas
Subject: Re: Presentations for the GLI - comments due April 27

Hi Émilie,

With respect to the presentation on the Canadian proposed LLP model, please add "Based on current approaches" to slide 6 for the environmental release text.

If you would like this elaborated further, or have any questions, please don't hesitate to let me know.

Sincerely,
Sarah

>>> Bergeron, Émilie<Emilie.Bergeron@AGR.GC.CA> 2015-04-22 4:45 PM >>>
Dear LLP colleagues

I am sending you 2 presentations that will be made by Canada during the upcoming GLI meeting 1) on Threshold Considerations and 2) the Canadian proposed LLP model. The presentation on threshold considerations is meant to reflect the document on threshold Canada prepared and circulated to the GLI members, this is not about our own Canadian considerations. As for the presentation on Canada proposed LLP policy, is to present our model and explain it once again to our friends from the GLI.
Your comments on both presentation are welcomed before Monday April 27, noon.

Thanks for your collaboration.

Émilie
773-1659

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13(1)(a), 19(1), 15(1)

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From: "Shearer,Heather [NCR]" <Heather.Shearer@ec.gc.ca>
To: "Nataliya Dormann" <Nataliya.Dormann@inspection.gc.ca>, "Martine de Graa...
CC: <sarah.davis@inspection.gc.ca>, <philip.macdonald@inspection.gc.ca>
Date: 2015/06/08 9:54 AM
Subject: Article on gene editing

Hello PBO,

Highly recommend you give this article a look - not technical, quick read, and raises some good points about regulating this technology (for example, interesting to think about gene drives to eradicate HT weeds)

http://www.nature.com/news/crispr-the-disruptor-1.17673

I hope everyone's doing well and enjoying the summer,

Heather

s.19(1)

From:
To:
Date: 2015/07/10 5:36 AM
Subject: SynBio discussions under the CBD

Dear All,

It has been a while since our last exchanges about the discussions on synthetic biology under the Biodiversity Convention (CBD).

As we discussed in our last conference call on this, given that the number of these informal discussion groups that are facilitated by PRRI keeps growing and that also the number of people participating in this groups keeps growing, PRRI will limit emails and conference calls to a 'need basis', indicated by requests from one or more of you.

After more than a month of relative - and relaxing - silence, we received the last two weeks several questions around two points: 1) what is the current situation on the on-line debates, 2) what next?

Below a quick update, but before doing so, first a welcome to some new people on this email list and a brief reminder of the objective of our exchanges: This is a group of colleagues with an interest in discussing Synthetic Biology in international fora such as OECD, CBD etc. The main aim is to exchange information and views. The exchanges in this group are informal, and not aimed at establishing common positions. Some colleagues on this list actively participate in the discussions, while others are mainly 'listeners'. PRRI participates facilitates similar groups on various CPB and CBD topics, such as environmental risk assessment, socio economic considerations in decision making, liability and redress, review and assessment. All these discussions are conducted under the Chatham House rules.

Returning to the debates under the CBD:

1. Current situation of the on-line debates.

The online discussions of are now over. For further details see: http://bch.cbd.int/synbio/calendar/.

The most recent online discussions (topics 6 and 7) focused on the following topics:

a) Which instruments exist that regulate the organisms, components or products derived from synthetic biology techniques?
b) Are these instruments adequate to address the potential impacts on the objectives of the Convention and its Protocols?

As people noted, the topics 6 and 7 overlapped quite a bit and in fact also duplicated earlier on line discussions.

In addressing topics 6 and 7, there were roughly two views: one view suggested that the current systems are not applicable and/or not adequate and that entirely new systems have to be set up for synthetic biology, while another view suggested that the current systems are applicable and adequate for now. I hold the latter view (I paste my post below).

As discussed with some of you, this debate goes beyond Synbio and takes place in many other areas such as genome editing.

As one of you noted: "the underlying question is why and how much regulation is needed, i.e. what safety problem needs to be fixed and how vulnerable is our safety?".

What we see in many of the posts in the online debate, many people have lost sight of why the original focus on GEOs/GMOs/LMOs: that focus was not because rDNA techniques were considered to confer risky characteristics per se, but based on the consideration that while conventional breeding and rDNA can both result in novel characteristics that can cause adverse effects, rDNA can make a broader range of novel combinations, with which there is limited experience. AS with food additives, societies have over the years taken the approach that it is wide ask in the case of things to which we may get exposed whether there are safety questions.

In short, the regulatory trigger in most regulatory frameworks and in the CPB is based a degree of novelty. (Notate bene: the fact that techniques are often linked to that definition of novelty is because conventionally produced organisms are by definition not considered to obtain that degree of novelty.) Once the novelty triggered scope is defined, the next step is choosing the regulatory instrument, which can range from a general condition that food should be safe (e.g. FDA), to a simple notification system, up to a full-fledged authorisation / certification system (e.g. EU, EPA, USDA). Yet, whatever the regulatory mechanism, case by case risk assessment plays a key role. As I mentioned to some of you, I plan to work with a number of colleagues from universities and research institutes the coming months to produce a number of papers that outlines the background and history of the objectives, scope (definitions), regulatory mechanisms and risk assessment in biosafety systems, so that they can use that in their discussions with their colleagues and authorities.

Will keep you posted on this.

*2. Next steps. *

The Secretariat is in the process of selecting experts to take part in the first face-to-face meeting of the AHTEG. AHTEG participants will be

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selected by the Secretariat, in consultation with the SBSTTA Bureau, from among those who were nominated by Parties, on the basis of their expertise and their participation in the Online Forum. A limited number of experts nominated by other Governments and organisations will be invited to take part in the AHTEG as observers. We understand that some of the people on this email have received an informal invitation checking their availability.

We will alert you once the appointed AHTEG members are published on the CBD site.

The first face to face meeting of the AHTEG is tentatively scheduled from 21 to 25 September 2015, in Montreal. Some of

We will come back with further updates early/mid September.

In the meantime we wish all the Northern Hemispherians a splendid Summer holiday.

PS: the Genetic Literacy Project has often interesting blogs on SynBio, e.g.:

http://www.geneticliteracyproject.org/2014/08/05/what-the-f-is-synthetic-biology/

http://www.geneticliteracyproject.org/2015/05/28/three-developments-that-will-help-synthetic-biology-to-live-up-to-its-promise/

Post on topics 6 and 7

Dear colleagues,

My name is

s.19(1)

My thanks to and for moderating the topics 6 and 7, which I take together in this post, as they are closely related as others have already said. I am pleased to see that many contributors follow the plea of Benson and Maria to be concise, and I will try to do the same.

Topic 6 is: "Adequacy of existing national, regional and/or international instruments to regulate the organisms, components or products derived from synthetic biology techniques".

As others have stated, this too broad a topic for an online discussion, as it would require a detailed analysis and discussion of national regulatory systems. I will therefore focus my contribution on the CBD, which in article 8g requires Parties to "....establish or maintain means to regulate, manage or control the risks associated with the use and release of living modified organisms....", and the Cartagena Protocol, which offers a tool for informed decision making about transboundary movements for countries that have not yet establish a national system as referred to in article 8g of the CBD.

Given that current and near future applications of synthetic biology involve the use of organisms with novel combinations of genetic material obtained through the use of modern biotechnological techniques that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection, the national systems as referred to in article 8g of the CBD as well as the Cartagena Protocol apply. As a consequence, the case by case risk assessments of those systems apply, for which Annex III of the CPB gives clear directions about the risk assessment, and for which a wealth of tools developed by other bodies are available.

There have been some posts that suggest that where synthetic biology is not explicitly mentioned in national biosafety regulations, new regulatory systems have to be developed. This is an erroneous conclusion, because the fact that a national regulatory system does not explicitly use the term "synthetic biology" (or any other biotechnological technique for that matter), does not necessarily mean that the organisms used in those techniques are not covered by the definition of LMO (or GMO as in Europe).

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There have also been posts that suggest that since the 'regulatory trigger' of the CBD and the CPB is a living organism and not non-living products, new regulatory systems have to be developed. I believe that this too quick a conclusion, because the sectoral product regulation (such as regulations for food, medicine, pesticides, et cetera) apply to the safety of those products. Those systems involve assessments, based on internationally agreed principles and methods developed under the Codex, the IPPC, the WHO etc.

In concluding, I concur with those colleagues who have said that at this point in time there is no need to establish additonal regulatory systems, but I also endorse those who have suggested that we should keep monitoring and exchanging information about applications of synthetic biology, to assess whether there will at one point in time be applications that warrant prior risk assessment but do not involve the use of organisms that are covered by the definition of LMO.

Best regards to all,

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Attachments removed further to discussion with applicant

Dylan Levac - Re: Fwd: Request: Articles for Plant Science Scan

From: Jaimie Schnell
To: Levac, Dylan
Date: 2015-08-26 8:57 AM
Subject: Re: Fwd: Request: Articles for Plant Science Scan
Attachments: CFIA_ACIA_-_#6738049_-_vR_-_PBRA_-_Science_Scan_-_Article_on_microRNAs_for_insect_resistant_crops_May_29_2015.DOCX.DRF

Sounds great, Dylan. It's an interesting area. I've attached an article submitted for the last science scan that you can use as a template. You can also take a look at a recent science scan to get an idea of the range in length of articles. Do you have the most recent? If not, I can send it to you.

Jaimie

>>> Dylan Levac 2015-08-26 8:06 AM >>>
Hi Jaimie,

I'll compose something about the CRISPR/Cas system for genome editing. There have been some great articles in this past year.

Are there any length/format criteria to follow?

Dylan

>>> Jaimie Schnell 2015-08-25 10:52 AM >>>
Hi Andrea and Dylan,

Brittany just sent out a new call for science scan contributions. Please see below for some additional information. If either of you find something interesting to write about, please let me know.

Jaimie

>>> Brittany Day 2015-08-25 10:43 AM >>>
Hi Andrea and Jaimie,

I am starting to prepare for the next edition of the Plant Science Scan and would like to ask that any contributions from the botany or biotech groups be sent to the Plant Science Scan email account (PSS-SSV@inspection.gc.ca) by Friday September 25th.

Just a reminder that all information communicated within the Plant Science Scan content must:

- Be part of the public domain. Sources may include:
  - Peer reviewed journals
  - Science based publications (e.g. Proceedings of the National Academy of Sciences)
  - Conference proceedings
  - Newsletters
  - Online resources: list-serves, databases, and real-time meta-searches (e.g. Google Alerts)

  - Other reliable materials and information resources (e.g. scientific posters)
- Not be the result of personal communication
- Not contain any sensitive or confidential business information
- Maintain the scientific and regulatory credibility of the CFIA

Cheers,

Brittany

Brittany Day
Project Coordinator - GAPP (Genomic Applications Partnership Program)
Plant Research and Strategies
Canadian Food Inspection Agency
1400 Merivale Rd. Tower 1
Ottawa, ON, K1A 0Y9
Brittany.Day@inspection.gc.ca / Tel: 613-773-5525

From: Cheryl Dollard
To: Schernthaner, Johann
CC: Davis, Sarah G.; Macdonald, Philip; Singh, Jas; Subramaniam, Gopal; ...
Date: 2015/09/03 2:57 PM
Subject: Re: Collaborative Research with AAFC

Dear Johann,

Thanks for your message. By way of this message, I would introduce you to Sarah Davis, National Manager of the Plant Biotechnology Risk Assessment Unit with CFIA, to weigh in on your questions regarding CRISPR technology and CFIA regulatory involvement in research in this area. Sarah will be able to discuss this with you more comprehensively.
Looking forward to this exchange,
With kind regards
Cheryl

Cheryl Dollard, MSc.

National Manager - Plant Health Laboratory Services/
Plant Research and Strategies
Plant Health Science Directorate - Canadian Food Inspection Agency
1400 Merivale Road Ottawa, Ontario K1A 0Y9

Please note my new phone number as of July 21, 2014: (613) 773-5117

cheryl.dollard@inspection.gc.ca
>>> "Schernthaner, Johann" <Johann.Schernthaner@AGR.GC.CA> 2015-09-03 1:51 PM >>>
Dear Cheryl,

STB has issued a call for LOIs for the 2016-2017 period. We are contemplating to propose a collaborative or complementary research proposal with CFIA provided our study subject is one of the priority issues for CFIA.

At ECORC, we are currently engaged in a project aimed at modifying bread wheat by means of genome editing using the CRISPR/Cas9 technology. Plants modified with this tool still qualify as PNTs in Canada, however, depending on the results of ongoing consultations being carried out in the EU and other countries regarding the regulation of CRISPRed plants, a likelihood exist that CRISPR genome edited plants could be considered as non-GMO suitable for unconfined release of Canadian genome edited crops in foreign markets.

The questions we have for you are:
- is there a CFIA interest in regulatory issues pertaining to CRISPR genome edited crops, and
- if so, would CFIA be interested in participating in this work either through direct collaboration or through complementary research?

We are very interested in your opinion in this matter.

Best regards,

Johann Schernthaner

Research Scientist
Eastern Cereal and Oilseed Research Centre
960 Carling Ave. K.W. Neatby Bldg.
Ottawa, Ontario K1A 0C6
Tel.: 613-715-5397
E-mail: Johann.Schernthaner@AGR.GC.CA

Cecile Girard - Biosafety research needs

From: Jaimie Schnell
To: Girard, Cecile
Date: 2015-09-23 10:04 AM
Subject: Biosafety research needs
Attachments: CFIA_ACIA_-_#6708163_-_vR_-_PR&S_Research_Needs_-_Biosafety_-_2015-16.XLSX.DRF

Hi Cécile,

Here's the spreadsheet with the biosafety research needs. As I suspected, there isn't one that would tie in easily with the CRISPR project.

I wasn't able to dig up Heather's presentation. I know someone sent it to me to view online, so if you're interested, you could probably check in with Cheryl or Brittany to see where the presentations are posted.

Jaimie

Working Group	Sub Group	Research Need ID	Research Need Title	Information Contact	Comments	Projects Addressing The Need (Internally and Externally Funded)	Cross linked to:
BIOSAFETY	Biology	0737	Collect baseline data on Canadian agro-ecosystems relevant to the environmental safety assessment of plants with novel traits, including tolerances of weeds and insects to pesticides, both plant expressed and applied, shifts in weed populations, prevalence and persistence of crop volunteers, biology of crop-weed hybrids and shifts in management practices.	Nataliya Dorman	Examples: Prairie weed surveys, Eastern Canada weed survey, baseline data studies on insect populations, baseline data studies on soil communities, weed shifts and management changes related to the adoption of herbicide tolerant cropping systems.	Beckie et al. 2013 "Herbicide-Resistant Weeds in the Canadian Prairies: 2007 to 2011" Weed Technology 27(1): 171-183.	
BIOSAFETY	Biology	1031	Fitness implications of interspecific hybrids resulting from gene flow from plants with novel traits platforms in Canada.	Sarah Davis	If research establishes that interspecific gene flow is possible, the next step is to determine if there is introgression of the trait into the related weedy species and/or species of concern. Any implications on fitness of hybrids may be dependant on the conferred trait and may need to be studied on a case-by-case basis.	**UofA-P-1301:** Fitness implications of introgression of novel traits from *Camelina sativa* to related species *C. microcarpa, C. alyssum* and *Capsella bursa-pastoris* (L. Hall UofA)	
BIOSAFETY	Biology	1222	Determine the relationship of glyphosate herbicide application with occurrence of diseases caused by *Fusarium* spp. or other pathogens.	Sarah Davis	Some studies have shown an association between glyphosate use and fusarium infections in the Canadian prairies however the nature of this association and the underlying mechanisms determining these effects are unknown. 'Plant pest potential' is one of the five pillars assessed when conducting risk assessments for unconfined environmental release of plants with novel traits (PNTs). These types of studies would inform the 'plant pest potential' pillar for glyphosate tolerant PNTs.	Work on the relationship of glyphosate to the prevalence of fusarium has begun at AAFC (Glyphosate associations with cereal diseases caused by *Fusarium* spp. in the Canadian Prairies, MR Fernandez *et al*. European Journal of Agronomy 31 (2009) 133-143)	
BIOSAFETY	Biology	PH0916	Baseline data on crop kinds used as platforms for PNTs	Sarah Davis	Information needed to support the creation of biological documents, risk assessment studies and the development of terms and conditions for confined research field trials on new crops (e.g. *Camelina sativa, Sorghum bicolor, Brassica carinata*)	**AAFC:** Advanced Genetic Technologies for Improvement of Camelina and Canola	
BIOSAFETY	New Technologies	1401	Evaluation of novel technologies, such as NGS, to characterize DNA inserts in plants. Validation of the protocols and data submitted for review. Issues include depth of sequencing, potential pitfalls, specific / required conditions, optimal representation of data.	Dylan Levac	Large agricultural companies such as Monsanto impliment their own protocols for eSouthern blots. In order to ensure comprehensive risk assessments, validation of these methods are required.	**CHA-P-1440 (GRDI):** Detection and Identifications of Plant Pests and Plants with Novel Traits using NGS Theme 6: PNTs Detection and ID (Donna Smith)	
BIOSAFETY	Pest mitigation	1423	Herbicide tolerance traits in *Camelina sativa*; stewardship recommendations for sustainable use.	Andrea Hitchon	Specific issues to explore include: rate of outcrossing to related weedy species, and whether such hybrids display herbicide tolerance		
BIOSAFETY	Pest mitigation	1030	Baseline data collection of Western/Northern corn rootworm and Western bean cutworm biology as it pertains to pesticide resistance, and particularly RNAi resistance, including (but not limited to) investigation(s) of developmental delays on RNAi products, lethality of current RNAi products on the marketplace, and inheritance of resistance.	Sarah Davis	Insect resistance management plans are becoming increasingly complex. Information on basic biology is urgently required to assess new proposals put forth by industry. Literature review required Non-target effect on likelihood of resistance; applications of RNAi, potential for gene targeting with RNAi targeting. Initial stage of research requires literature review.	**UofG-P-1301**: Development of a standardized resistance monitoring bioassay for corn rootworm (A. Schaafsma UofG)	
BIOSAFETY	Pest mitigation	PH0919	Develop and evaluate experiments to predict the invasiveness of potential new plant platforms in Canada.	Sarah Davis	There is a need for experimental designs and protocols to assess the potential invasiveness/weediness of new species to Canada.	Linda Hall (U of Alberta) with Hugh Beckie (AAFC) have begun a project to examine replacement rate as a parameter of invasiveness.	IAS
BIOSAFETY	PNT Control	1433	For major crops (e.g. canola, camelina, corn, soybean and wheat), categorize the outcrossing rate in a sink population when the size of the source population increases, at a distance equivalent to the isolation distances used in the confined research field trial (CRFT) program	Edward Harrison	Considering standard CRFT terms and conditions, and reproductive biology specific to certain crops, determine what would, be the maximum acreage that could be planted with PNT in the context of the CRFT program, without compromising confinement of the novel traits. Additional data on pollen flow pattern (outcrossing) when the source population increases are needed.		
BIOSAFETY	PNT Control	1221	Determine secondary dormancy potential of *Brassica juncea* and to support the confined field trials of plants with novel traits program.	Edward Harrison	Currently, a 5 year post-harvest monitoring period is required for *B. juncea* confined field trials. It has been proposed to reduce the post-harvest monitoring period of *B. juncea* from 5 years to 3 years similar to *B. napus*. However, there is not enough empirical data available to fully inform on secondary dormancy of *B. juncea*.		
BIOSAFETY	PNT Control	1301	Optimize/validate methods for the detection and characterization of plants with novel traits that are not authorized in Canada for use in monitoring of imports for low-level presence of unauthorized events, as per Government of Canada policies. The events considered may be based on the likelihood of import of low level presence of that event.	Cindy Pearson	The research required to address specific methods may be determined using intelligence regarding products of biotechnology authorized outside of Canada and likelihood of import of these products into Canada	**CHA-P-1440 (GRDI):** Detection and Identifications of Plant Pests and Plants with Novel Traits using NGS Theme 6: PNTs Detection and ID (Donna Smith)	

Cecile Girard - Re: Fwd: Collaborative Research with AAFC/ECORC

From: Cecile Girard
To: Schnell, Jaimie
Date: 2015-09-23 11:44 AM
Subject: Re: Fwd: Collaborative Research with AAFC/ECORC
Attachments: CFIA_ACIA_-_#7211532_-_vR_-_Science_Scan_-_The_CRISPR_craze.DOCX.DRF; Bortesi Fischer 2015.pdf; Zhang et al 2014.pdf

>>> Dylan Levac 2015-09-23 10:16 AM >>>
Hi Cecile,
The article I've written for the next Science Scan issue is on the CRISPR/Cas genome editing molecular tool set. I've provided the link to that RDIMS file.

I wouldn't consider myself an authority on the subject as I've never worked with the technology, but I've read most of the plant CRISPR/Cas literature.

My impression is that CRISPR/Cas is an amazing, emerging technology. It has the potential to generate homozygous, gene edited plant varieties in a single generation.

Regarding the intention of this funding request; this is exactly where there is little information on CRISPR/Cas. With the exception of one report in rice (Zhang *et al.* 2014), there is almost no comprehensive or robust analysis of off-target effects of the system. The whole-genome sequencing of rice modified through CRISPR/Cas did show no off-target effects, however. So at this point there seems to be little worry about off-target effects.

Anyway, I've attached a nice review of the CRISPR/Cas system for plant genome editing, and the rice reference.

Best wishes,
Dylan

>>> Cecile Girard 2015-09-23 9:40 AM >>>
Hi Dylan and Jaimie

I'll touch base with Sarah when she returns, however I wanted to give you the heads up. Are you familiar with CRISPR?

>>> "Schernthaner, Johann" <Johann.Schernthaner@AGR.GC.CA> 2015-09-22 2:27 PM >>>
Dear Sarah,

As Cheryl recommended you as the contact person in this matter, I am resending our request to you:

We are planning to submit an LOI to the AAFC Proposal Submission System to request funding for research to

determine the efficiency and accuracy of CRISPR genome editing in crops. As you are aware, CRISPR has become the gold standard for genome editing not just in medical research but also in plant biology for basic research as well as the generation of desired phenotypes. In our conversation with EU regulatory representatives (at the Rapeseed Congress, Saskatoon, July 2015), the understanding is that there is a high probability that CRISPR editing will be regulated as non-GMO in most EU jurisdictions. The CRISPR method could therefore open a significant market to Canadian crop exporters.

Presently, our labs are involved in ongoing research employing CRISPR technology in an attempt to edit plant genomes in order to study proteins related to pathogen resistance. Our experience in using this technology and the resources we have built could be easily transferred to the proposed project.

Specifically, the project would be about applying currently existing variations of the CRISPR/Cas method to Brassica and wheat and then to ascertain the frequencies and precision of the mutagenesis with respect to target gene versus off-target gene mutations in a statistical fashion. As Canada regulates PNT release by product rather than process, such information will also be informative to CFIA in regulatory decisions.

Such a project could be done either in direct collaboration or, if that is not feasible, by stating your support in form of a support letter.

We look forward to your response.

Best regards,

Johann Schernthaner
Research Scientist
Eastern Cereal and Oilseed Research Centre
960 Carling Ave. K.W. Neatby Bldg.
Ottawa, Ontario K1A 0C6
Tel.: 613-715-5397
E-mail: Johann.Schernthaner@AGR.GC.CA<mailto:Johann.Schernthaner@AGR.GC.CA>

Begin forwarded message:

From: Cheryl Dollard <Cheryl.Dollard@inspection.gc.ca<mailto:Cheryl.Dollard@inspection.gc.ca>>
Subject: Re: Collaborative Research with AAFC
Date: September 3, 2015 at 14:57:13 GMT-4
To: Johann Schernthaner <Johann.Schernthaner@AGR.GC.CA<mailto:Johann.Schernthaner@AGR.GC.CA>>
Cc: Jas Singh <Jas.Singh@AGR.GC.CA<mailto:Jas.Singh@AGR.GC.CA>>, Gopal Subramaniam <Rajagopal.Subramaniam@AGR.GC.CA<mailto:Rajagopal.Subramaniam@AGR.GC.CA>>, Christine Tibelius <Christine.Tibelius@inspection.gc.ca<mailto:Christine.Tibelius@inspection.gc.ca>>, Philip Macdonald <Philip.Macdonald@inspection.gc.ca<mailto:Philip.Macdonald@inspection.gc.ca>>, "Sarah G. Davis" <Sarah.Davis@inspection.gc.ca<mailto:Sarah.Davis@inspection.gc.ca>>

Dear Johann,

Thanks for your message. By way of this message, I would introduce you to Sarah Davis, National Manager of the Plant Biotechnology Risk Assessment Unit with CFIA, to weigh in on your questions regarding CRISPR technology and CFIA regulatory involvement in research in this area. Sarah will be able to discuss this with you more comprehensively.
Looking forward to this exchange,
With kind regards

Cheryl

Cheryl Dollard, MSc.

National Manager - Plant Health Laboratory Services/
Plant Research and Strategies
Plant Health Science Directorate - Canadian Food Inspection Agency
1400 Merivale Road Ottawa, Ontario K1A 0Y9

Please note my new phone number as of July 21, 2014: (613) 773-5117

cheryl.dollard@inspection.gc.ca<mailto:cheryl.dollard@inspection.gc.ca>
>>> "Schernthaner, Johann" <Johann.Schernthaner@AGR.GC.CA<mailto:Johann.Schernthaner@AGR.GC.CA>>
2015-09-03 1:51 PM >>>
Dear Cheryl,

STB has issued a call for LOIs for the 2016-2017 period. We are contemplating to propose a collaborative or complementary research proposal with CFIA provided our study subject is one of the priority issues for CFIA.

At ECORC, we are currently engaged in a project aimed at modifying bread wheat by means of genome editing using the CRISPR/Cas9 technology. Plants modified with this tool still qualify as PNTs in Canada, however, depending on the results of ongoing consultations being carried out in the EU and other countries regarding the regulation of CRISPRed plants, a likelihood exist that CRISPR genome edited plants could be considered as non-GMO suitable for unconfined release of Canadian genome edited crops in foreign markets.

The questions we have for you are:
- is there a CFIA interest in regulatory issues pertaining to CRISPR
genome edited crops, and
- if so, would CFIA be interested in participating in this work either through direct collaboration or through complementary research?

We are very interested in your opinion in this matter.

Best regards,

Johann Schernthaner
Research Scientist
Eastern Cereal and Oilseed Research Centre
960 Carling Ave. K.W. Neatby Bldg.
Ottawa, Ontario K1A 0C6
Tel.: 613-715-5397
E-mail: Johann.Schernthaner@AGR.GC.CA<mailto:Johann.Schernthaner@AGR.GC.CA>

Dylan Levac

The CRISPR Craze

In Nature, clustered regularly interspaced palindromic repeat (CRISPR) arrays confer adaptive, pathogen immunity to bacteria. This form of immunity has been re-developed for biotech purposes and lends itself well to editing genomic sequences. Since 2013, genome editing using CRISPR-Cas9 tools has been reported for ten plants; notable crops are rice, sorghum, tomato, tobacco, wheat, maize, and sweet orange. The hopes are that the lowered costs of CRISPR-Cas9 tools, in comparison to existing sequence specific nucleases (SSN), and the democratization of these tools will lead to improving crops like cassava, which are important in the developing world.

The recent explosion of interest in CRISPR-Cas9 tools can be traced to its features; Firstly, CRISPR-Cas9 SSN target DNA using a guide RNA (gRNA) and Watson-Crick pairing rules. By comparison, other SSNs, like zink finger nucleases (ZFN) and transcription activator-like effector nucleases (TALEN), use protein-based DNA interactions which are more costly and difficult to engineer. Secondly, no cloning is required for CRISPR-Cas9 constructs, and multiple genomic loci can be targeted in a single experiment. These two features dramatically improve the throughput of genome editing programs over other SSNs. Furthermore, CRISPR-Cas9 tools can be used to perform targeted insertion-deletion mutations, as well as introduce exogenous DNA from distantly related organisms. And lastly, in contrast to the proprietary nature of ZFNs, the CRISPR-Cas9 technology is open-access. Resources like plasmid requisition, gRNA specificity prediction tools, and support and discussion forums are available online. These features make the CRISPR-Cas9 system dramatically less expensive to execute and can be more easily developed in new labs when compared to other SSNs.

In terms of applications; one might imagine scientists producing, in a single generation, a low cyanogenic glycoside cassava plant by disrupting every gene involved in cyanogenic glycoside biosynthesis. This is theoretically possible with CRISPR-Cas9 tools. This cassava product would have improved nutritional value and reduced post-harvest costs.

It remains to be seen how products of CRISPR-Cas9 tools will be treated by worldwide regulatory agencies. Where these tools are used for targeted mutagenesis purposes, the genome alterations are indistinguishable from those that naturally occur during plant breeding, and this plant product might be regulated as chemically mutated plant varieties are. Where exogenous DNA sequences are introduced, one might imagine that those plant products will be treated similarly to other products of recombinant DNA technologies. Because the Canadian regulatory system is product based, we are well positioned to address plants generated by this remarkable technology.

Bortesi, L., Fischer, R., 2015, The CRISPR/Cas9 system for plant genome editing and beyond, Biotechnology Advances, 33, 41-52

Van der Oost, J., Westra, E., Jackson, R., Wiedenheft, B., 2014, Unravelling the structural and mechanistic baisis of CRISPR-Cas systems, Nature Reviews Microbiology, 12, 479-492

Voytas, D., Gao, C., 2014, Precision genome engineering and agriculture: opportunities and regulatory challenges. PLOS Biology, 12:6, e1001877. doi:10.1371/journal.pbio.1001877

Cecile Girard - CRISPR Gene Drives

From: Jaimie Schnell
To: Girard, Cecile; Levac, Dylan
Date: 2015-09-23 3:49 PM
Subject: CRISPR Gene Drives
Attachments: PNAS-2015-Webber-10565-7.pdf

Hi Dylan and Cécile,

Since we've been talking about CRISPR a lot all of a sudden, I thought I would share a specific application of the CRISPR technology that has garnered some interest/concern: gene drives. They are primarily being considered for applications such as mosquito control, but the attached paper also discussing using them to control invasive species. I've also seen at least one reference to using such gene drives to reverse the development of resistance, which is one that is more directly applicable to our work.

Incidentally, this is one topic under consideration for the 2017 ISBGMO (Cécile, I don't think I've had the change to mention this to you yet, but I'm on the scientific committee for the ISBGMO).

Jaimie

Sarah G. Davis - Re: Further info on the outcomes of the AHTEG on Synthetic Biology

From: Sarah G. Davis
To: Girard, Cecile; Macdonald, Philip; Schnell, Jaimie; Tibelius, Christine
Date: 2015-10-09 11:34 AM
Subject: Re: Further info on the outcomes of the AHTEG on Synthetic Biology

Hi Jaimie,

Thank-you very much for that comprehensive overview. Point 3 below makes me wonder about the role that non-peer reviewed publications will play. I'm (naively) surprised that there wouldn't be more consensus on a science-based approach to information gathering. At any rate, I sincerely appreciate you keeping us in the loop as these conversations continue to evolve.

Sarah

>>> Jaimie Schnell 2015-10-07 11:34 AM >>>
Hi all,

I participated in a conference call with Jim Louter to listen to a verbal debrief of his participation in the AHTEG on Synthetic Biology. There were a few points that I thought were worth highlighting for you all. They're all in relation to the draft report of the AHTEG, which I've attached here.

1) Paragraph 24 includes the operational definition of Synthetic Biology. Jim pointed out that use of the term "modern biotechnology" in the definition gives it firm linkages to the Cartagena Protocol, in which modern biotechnology is defined in fairly narrow terms [*the application of: a. In vitro nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles, or b. Fusion of cells beyond the taxonomic family, that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection.*] This was preferred over biotechnology, which is defined much more broadly in the CBD [*any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use*].

2) For organisms derived from synthetic biology, there was general agreement that these will fall under the definition of LMOs and be covered by the Cartagena Protocol and overall there is a comprehensive framework in place (e.g., paragraphs 34 and 38). Jim mentioned that no one at the AHTEG could come up with a real example of an organism of synthetic biology that wouldn't be an LMO. However, there are a few places in the document where this is undermined, such as paragraphs 35 and 79.

3) Jim mentioned that there was a strong push, particularly by the NGOs, to equate non-peer reviewed publications (e.g. blog posts, website content, self-published articles) with peer-reviewed publications in terms of their value. See for example paragraph 46, which mentions that synthetic biology should be assessed with an appropriate balance between evidence as well as rational arguments. "Rational arguments" could be interpreted quite loosely by NGOs.

4) It was agreed that components and products of synthetic biology are non-living and therefore do not fall under the scope of the Cartagena Protocol (Paragraph 33). It was unclear if there were potentially gaps in oversight for products and components of synthetic biology. It was discussed that oversight likely existed, e.g. for chemicals, drugs, cosmetics, etc., but there is no single, overarching framework and so oversight is described

as fragmented. Similarly, it was noted that there could be gaps in oversight under the Convention and its Protocols for components and products of synthetic biology. Jim was of the opinion that we likely had sufficient systems in place since products of synthetic biology would be equivalent to their non-synthetic biology counterparts and would be regulated similarly.

Jim expects that a new draft AHTEG report will be circulated to AHTEG members for review that should take on board final discussions. Much of the mark up in the attached document should be reflected in the next iteration. Following this, there should be additional activity at SBSTTA20 [Subsidiary Body on Scientific, Technical and Technological Advice], which is April 25-29, 2016.

Regards,
Jaimie

From: Luc Bourbonniere <Luc.Bourbonniere@hc-sc.gc.ca>
To: Jordan Bean <jordan.bean@hc-sc.gc.ca>, Neil Strand <neil.strand@hc-sc.gc...
Date: 2015/10/19 9:32 AM
Subject: Jennifer Doudna (UC Berkeley / HHMI): Genome Engineering with CRISPR-Cas9

Another good site on youtube: iBiology

https://www.youtube.com/watch?time_continue=120&v=SuAxDVBt7kQ

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From:
To:
CC:
Date: 2015/10/26 7:44 PM
Subject: Re: SynBio - update

I agree with your position,

On Mon, Oct 26, 2015 at 5:52 PM,
wrote:

> Hi thanks for the thoughts.
>
>
>
> As gene editing via small deletions are not discernible from mutations
> that we have not found in nature yet, I would argue that these not be
> regulated differently than conventional breeding, i.e we just haven't found
> it yet, regardless of what process used.
>
>
>
> Similarly null segregants, those that do not contain the transgene should
> not be regulated. This is the stance of course for the everywhere but EU.
>
>
>
> Best,
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> *From:*
> *Sent:* Monday, October 26, 2015 11:31 AM
> *To:*
> *Cc:*
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>
> *Subject:* Re: SynBio - update

Philip Macdonald;

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>
> Just now taking some time to digest what you wrote here regarding the
> definition of GMO/LMO and new breeding techniques, so my commentary here is
> intended more to improve my understanding than to take a position. While
> the definition of GMO/LMO seems in principle to be based on process *and*
> novelty, I would be interested to know how the CPB and the EU would deal
> with these two cases in practice: 1) an organism produced by transgenesis
> but expressing a non-novel trait (e.g. a transgenic plant where a native
> gene is introduced from one variety to another because it would be more
> rapid than breeding), or 2) an organism produced by chemical or radiation
> mutagenesis that expresses a novel trait.
>
>
>
> Relating to the CPB definition, case 1 possesses a non-novel combination
> of genetic material even though it is obtained through the use of modern
> biotechnology. Case 2 possesses a novel combination, but not through
> modern biotechnology. I would assume case 1 would be treated as an LMO,
> but case 2 would not? If that is the case, then process trumps novelty in
> the definition. So if gene editing techniques were employed to produce
> case 1, would case 1 still be an LMO, because it is captured by the "modern
> biotechnology" element? If so, then process would trump novelty again.
>
>
>
> Relating to the EU definition, case 1 is an organism in which the genetic
> material has *no*t been altered in a way that does not occur naturally by
> mating and/or natural recombination (I'm actually now having trouble
> parsing our this definition). Case 2 has been altered by a process that
> results in a combination that does *not* occur naturally by mating and/or
> natural recombination. I would assume however that in the EU, case 1 would
> still be treated as a GMO, while case 2 would not? Likewise process trumps
> novelty in both cases. To me the hope that is offered by the EU definition
> is that one can argue the process of gene editing makes use of natural
> recombination processes (non-homologous end-joining and repair, for
> example) and therefore could be used to exempt both cases from the GMO
> definition.
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> On Sat, Oct 24, 2015 at 9:57 AM,

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> Dear All,
>
> I follow up on our communications about the Synthetic Biology discussions
> under the CBD.
>
> Quick update and request for feedback:
>
> *AHTEG SYNBIO *
>
> The first AHTEG on SynBio took place from 21 to 25 September in Montreal.
> Several people on this email list participated in that AHTEG.
>
> The feedback shows that this process was an eye-opener for many, at times
> frustrating for some, but that nevertheless the resulting report is found
> to be fairly balanced in that it reflects the various views on the topics:
>
> - Relationship between synthetic biology and biological diversity;
>
> - Similarities and differences between LMOs and SynBio
>
> - Adequacy of existing regulatory instruments to address SynBio;
>
> - Operational definition of synthetic biology;
>
> - Potential benefits and risks to the conservation and sustainable use of
> biodiversity
>
> - Best practices on risk assessment and monitoring;
>
>
>
> We will inform you when the final report is posted on the CBD site. The
> report of the AHTEG will be submitted to the SBSTTA (see below).
>
> As the AHTEG documents and discussion show, there are many links to topics
> under the Cartagena Protocol, e.g.:
>
> - definitions
>
> - Environmental Risk Assessment
>
> - Socio – Economic considerations
>
>
>
> As regards definitions, I draw your attention to a discussion we have in
> Europe on the definition of a GMO in relation to New Breeding Techniques. I
> attach below for your information an email exchange with my colleagues in
> Europe. Main message is that while the definitions of GMO and LMO refer to
> certain techniques, the decisive element in those definitions is whether
> the resulting organisms possess novel genetic combinations, i.e. genetic
> combinations that "do not occur naturally by mating or recombination" (as
> phrased in the EU) or "overcome natural physiological reproductive or
> recombination barriers" (as phrased in the CPB). In short, these

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> regulations are not 'process based', because both the use of the technique
> and the novelty of the resulting genetic combinations are relevant. This
> discussion will also be relevant for SynBio.
>
> As to Environmental Risk Assessment and Socio–Economic considerations, we
> have similar informal discussion groups on those CPB topics and will keep
> you posted of relevant developments there.
>
>
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>
>
> *SBTTA *
>
> The result of the on line discussion and the report of the AHTEG will be
> submitted to the Subsidiary Body on Scientific, Technical and Technological
> Advice. The first upcoming meeting of the SBSTTA is SBSTA-19 from 2 - 5
> November 2015, Montreal. The next SBSTTA will be from 25 - 29 April 2016
> in Montreal.
>
> The topic is included on the agenda of SBSTTA-20, in April 2016. (see:
> https://www.cbd.int/doc/?meeting=SBSTTA-20).
>
> It will be very good if some of us who participated in the on line
> discussions and/orteh AHTEG can participate.
>
>
>
> *COP13 *
>
> The COP13 will be held from 4 - 17 December 2016, in Cancun.
>
> (See: https://www.cbd.int/doc/?meeting=COP-13).
>
>
>
> As discussed, in addition to being prepared for the negotiations, it will
> be good to hold a side event on SynBio during COP13, preferably including
> young students (e.g. the iGEM initiative). and
> have already indicated to be willing to help with that. We will keep you
> posted on that.
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> Wishing you all a great remainder of the weekend !
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> Dear All,
>

> Many thanks for your responses to my emails about the EU/CPB definitions
> of GMO/LMO, and the implications for organisms developed by New Breeding
> Techniques (NBTs).
>
> As several more people have been added to this list, let me briefly
> summarise:
>
> While these definitions refer to certain techniques, the decisive element
> in those definitions is whether the resulting organisms possess novel
> genetic combinations, i.e. genetic combinations that "do not occur
> naturally by mating or recombination" (as phrased in the EU) or "overcome
> natural physiological reproductive or recombination barriers" (as phrased
> in the CPB).
>
> In short, these regulations are not 'process based', but rather both the
> use of the technique *and* the novelty of the resulting genetic
> combinations are relevant.
>
> This is concisely reflected in the CPB definition: "an LMO is a living
> organism that 1) possesses a novel combination of genetic material 2)
> obtained through the use of modern biotechnology".
>
> In the EU definition this phrased a bit more opaquely with "*an organism
> in which the genetic material has been altered in a way that does not occur
> naturally by mating and/or natural recombination*". Over the years there
> has been some discussion as to whether "altered in way" refers to the
> technique, to the end result, or to both. As I illustrated in my previous
> emails, the definition and the annexes that belong to that definition shows
> that this "altered in a way" refers to both the technique used and the
> novelty of the genetic combination obtained.
>
> This interpretation is nothing surprising, because this notion of
> 'novelty' has been the consistent element since the first definitions in
> the mid-80s, and (as the European Commission has stated) the EU GMO
> definition is consistent with the definition of the CPB.
>
> Some of you have expressed concern that nevertheless the EC may follow a
> purely 'process based' interpretation. That seems unlikely, if you see for
> example what Commissioner Borg said in reply to questions from MEPs: " .....
> the definition of GMO in the EU legislation is referring both to the
> characteristics of the organism obtained and to the techniques used....". See
> link
> <http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-%2f%2fEP%2f%2fTEXT%2bWQ%2bE-2014-006525%2b0%2bDOC%2bXML%2bV0%2f%2fEN&language=EN>.
> In addition, several EU Competent Authorities have written to the EC that
> they are of the view that the EU definition of a GMO relies *both* on the
> process used and the resulting organism/product.
>
> Last but not least, your responses confirm that most – if not all – of you
> endorse the view that a purely technique based interpretation would make
> little sense.
>
> What our email-exchanges have also taught us is that it is important to
> make clear whether we are expressing what we think the definition says, or
> whether we express what we think others believe what the definition says.
>

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> Turning to organisms produced through NBTs: as said, for a meaningful
> discussion it is important to make clear to which NBTs we are referring,
> because genome editing techniques are for example very different from DNA
> methylation techniques, again different from Agroinfiltration, etc. etc.
>
> As regards the question to what extent organisms produced through specific
> NBTs fall under the GMO/LMO definition: the answer to that question depends
> on whether these techniques have resulted in novel genetic combinations,
> i.e. combinations that go beyond natural mating or recombination / natural
> physiological reproductive or recombination barriers
>
> Such a nuanced approach is also reflected in the report of the WGNT, which
> for example for the ZFN technique made a distinction in FSN1, FSN2 and FSN
> 3, based on the extent of the alteration.
>
> See also the attached letter of EFSA to the European Commission of 15
> October 2015. While I believe that some details in that letter would need
> some further discussion, the overall approach confirms the notion that when
> talking about definitions the resulting organisms need to be taken into
> account. What I also find very important in the EFSA letter is the
> statement that we should remain aware that this field evolves rapidly. I
> fully endorse the notion that we should keep monitoring future
> developments, and I believe that in doing so we should look beyond NBTs,
> and also look at areas as Synthetic Biology (see some articles below this
> email), e.g. what about XNA?
>
> As discussed, with the rapid development of new techniques and with the
> increasing knowledge of genomic variability, the challenging task is of
> course to fine tune the grey areas, which would be a great topic for a
> scientific brainstorm workshop to discuss 'how novel is novel' and related
> topics.
>
> We have received many enthusiastic reactions to the idea of holding such a
> workshop, and a few of you have already prepared the attached draft
> info-sheet for CRISPR, that can be used in the discussions. Please keep
> that draft info-sheet to yourselves for now.
>
> We have fixed the workshop on 9 December, at the Free University of
> Brussels. Program and details will follow.
>
> Please send me at the latest on 5 November your interest in participation
> (repeated request: please do not copy everyone to avoid clogging of
> inboxes). For those who cannot cover their travel from their own budgets,
> we have secured some extra travel funds with the help of
>
> Looking forward to hearing from you
>
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>
> PS: Below some recent articles on NBTs.
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> Faculty of Sciences, Faculty of Law, Ghent University, Belgium
>
> Faculty of Science and Bio-Engineering Sciences, Free University Brussels
> (VUB
> <https://caliweb.cumulus.vub.ac.be/caliweb/?page=course-offer&id=008938&anchor=1&target=pr&year=1415&language=en&output=html>),
> Belgium
>
> c/o International Plant Biotechnology Outreach (IPBO)
> <http://ipbo.vib-ugent.be/team, IIC/UGent
>
> Technologiepark 3, B-9052 Gent-Zwijnaarde, Belgium
>
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> The Economist | Gene editing: Even CRISPR:
> http://www.economist.com/news/science-and-technology/21668031-scientists-have-found-yet-another-way-edit-genomes-suggesting-such-technology-will?frsc=dg%7Ca
>
>
>
> *Wired** covers Monday's National Academy of Sciences meeting on human
> genome editing*
>
> *Wired:* Science Would Like Some Rules for Genome Editing, Please
> <http://www.wired.com/2015/10/science-like-rules-genome-editing-please/>
>
>
>
> *Science:* Four synthetic biology inventions that flummox the feds
> <http://news.sciencemag.org/scientific-community/2015/10/four-synthetic-biology-inventions-flummox-feds?utm_campaign=email-news-weekly&et_rid=35367769&et_cid=51999>
>
> *Wilson Center:* The DNA of the U.S. Regulatory System: Are We Getting It
> Right for Synthetic Biology?
> <http://www.synbioproject.org/publications/dna-of-the-u.s-regulatory-system/>
>
> *Bloomberg View:* This Is No Way to Regulate GMOs
> <http://www.bloombergview.com/articles/2015-10-21/this-is-no-way-to-regulate-genetic-modification>
>
> *Nature* (news): CRISPR tweak may help gene-edited crops bypass biosafety
> regulation
> <http://www.nature.com/news/crispr-tweak-may-help-gene-edited-crops-bypass-biosafety-regulation-1.18590>
>
> *Nature Biotechnology:* DNA-free genome editing in plants with
> preassembled CRISPR-Cas9 ribonucleoproteins
> <http://www.nature.com/nbt/journal/vaop/ncurrent/full/nbt.3389.html>
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>

Sarah G. Davis - Re: Fwd: Testing the Roadmap - workshop being organized by Dr. Karen Hokanson

From: Sarah G. Davis
To: Tibelius, Christine
Date: 2015-10-27 1:09 PM
Subject: Re: Fwd: Testing the Roadmap - workshop being organized by Dr. Karen Hokanson

Hi Christine,

Sounds great. Phil is the resident expert on all things Road Map related, so I've set-up a meeting between the three of us so he can fill us in.

Related to your note below, I'd be very interested in two topics related to PBRA's budget:

1. Is some of PBRA's $42,500 budget being re-distributed to Rob's team? I remember you mentioning this was a possibility, but I'm not sure what decision arose.
2. Has there been any discussion about Dylan's future? As a reminder, his terms expires Given November is just around the corner, I thought it might be useful to touch base on that front.

Incidentally, France and I will be meeting later this week to make sure our budget tracking aligns.

Thank-you!
Sarah

>>> Christine Tibelius 2015-10-27 11:35 AM >>>
Hi Sarah,

I'd like to have a bit more background on the Roadmap. On the budget side, France and I are meeting this week to see where things sit for the Division in terms of where we are with expenditures and commitments.

Christine

>>> Sarah G. Davis 2015/10/27 10:59 AM >>>
Good morning,

Please see email below.

Phil, as a major dissenting voice in the development of the Road Map, do you think my participation in this activity would be of value? Your honest opinion is appreciated! :)

Christine, obviously this workshop isn't on the event plan nor in my current budget, so perhaps we could chat about whether it would be feasible for me to attend, provided Phil advocates for it. It's being held in Washington, so presumably it would cost approximately $2000. A lot of PBRA travel is happening this fall, so I should have a better snapshot of my budget once those activities are completed.

Sarah

>>> 2015-10-27 8:15 AM >>>

Hi Sarah,

I hope that things are well in Ottawa. I wanted to make an introduction and invite you to a workshop that is being organized for the first week of February next year. The workshop is an attempt to have experienced risk assessors review the Road Map produced by the AHTEG under the Cartagena Protocol in order to provide their feedback. The activity is being funded by a grant from USDA's Biotechnology Risk Assessment Research Grants (BRAG) program, and the award is being managed by (copied here) at the University of Minnesota.

Although it is not an ILSI supported activity, we will be providing meeting space at our offices in Washington as a public service and has asked if I would help out a bit with the organization of the workshop and by extending some informal invitations (like this one). So, let me know if this is something you would be willing and able to participate in. As the National Manager for the PBRA unit your participation would be of tremendous benefit for the activity, and I think your ability to function well in the context of a group discussions will be a big asset as well.

If you have any questions let me know. I'm sure would also be happy to provide any additional details you need regarding the workshop.

Best,

Center for Environmental Risk Assessment
&
Center for Safety Assessment of Food and Feed
ILSI Research Foundation
tel: 202-659-3306 ext.

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From: Philip Macdonald
To: Sarah G. Davis
Date: 2015-11-12 3:50 PM
Subject: Fwd: Re: FW: GIC Risk Assessment Workgroup: Summary of 4 November 2015 Conference Call
Attachments: CPB RA Meeting Concept Note.docx

fyi

>>> 2015-11-12 1:02 PM >>>
Hi

Thanks for sending this. These look like good points to me.

Just as an update for all of you, plans are still in progress for a meeting in February, where our 'experienced' risk assessors who have expressed concern regarding the roadmap and the need for 'technical consensus' (as put it) can have a discussion and develop some recommendations. I think everyone on this message is aware of this meeting. The latest version of the Concept Note is attached. It is now scheduled for the first week in February (in DC).

We are viewing this meeting in February as an opportunity to at least reach some consensus from among the 'like-minded' group of experienced regulators about where the roadmap captures what IS commonly found in 'actual' cases of risk assessment, and where it truly delves into the 'fairy tale' realm, or where it varies by country.

Of course, it will be necessary to take stock after the face-to-face meeting of the AHTEG next week of what changes have been incorporated (if any) into the roadmap, so we can take that into consideration during our February discussion.

There are only two people on the 'to be confirmed' list for the February meeting who are currently members (from parties) on the AHTEG: from South Africa and from Japan. Neither of these have been officially invited to the meeting yet (although knows about it). We have decided it will be better to engage these two more fully after the AHTEG meeting.

I don't necessarily want to keep the February meeting a secret from and the rest of the AHTEG, but I also don't want to give them any impression that they can participate. So, I don't plan to offer it as a way forward or to present anything about it while we are there next week. I hope you agree.

Having said that, I do hope that those of us on this message can find a time to talk about the February meeting while we are together, especially toward the end of next week, so we can think about any changes to our approach based on what is discussed at this AHTEG meeting. (Come to think of it - there should be plenty of down time when we are banned from the AHTEG meeting, if it is anything like the last one in Bonn.)

Phil, we have also been in touch with Sarah Davies about participating. Do not know if you know this.
and

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we have been in touch with [redacted] and he is interested, but he did indicate that he might send you, if he can not attend. Not sure if he communicated this to you.

Let me know your thoughts.

Thanks,

On Thu, Nov 12, 2015 at 10:28 AM, [redacted] > wrote:

> FYI - the following are some talking point I developed on the subject of
> advancing work on additional guidance. Please let me know what you think
> of them.
>
>
>
> Thanks,
>
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>
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>
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>
>
>
> Ubi caritas, ibi iustitia.
>
>
>
> *From:*
> *Sent:* Wednesday, November 11, 2015 2:19 PM
> *To:*
> *Cc:*
> *Subject:* RE: GIC Risk Assessment Workgroup: Summary of 4 November 2015
> Conference Call
>
>
>
>
>
> Talking points:

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>
>
>
> Many AHTEG members and participants in the on-line forum have consistently
> stated that work on additional guidance is premature until a final roadmap
> is welcomed by the MOP. Building additional guidance based on draft text
> is inappropriate and creates an unwelcome diversion to finishing the
> roadmap.
>
>
>
> Many members of the AHTEG are deeply concerned about the process used in
> the open-ended forum. The texts produced and discussed are the outcome of
> a negotiation rather than a consensus among technical experts. As such,
> the process can only produce "chair's text" representing a compromise as
> understood by the chair of the AHTEG.
>
>
>
> We strongly urge that the process led by the Secretariat seek technical
> consensus on the roadmap first; and only thereafter undertake work to
> extend the principles within the roadmap to guidance as prioritized in
> other conversations.
>
>
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University of Minnesota, St. Paul, MN 55108
Phone:
E-mail:
sbc.umn.edu <http://www.sbc.umn.edu/>

CONCEPT NOTE

Meeting to Review the Process for Risk Assessment under the Cartagena Protocol for Biosafety

Based on their experience with risk assessment and approvals of GM crops, participants are invited to a small, focused meeting to evaluate and discuss the 'Roadmap' that has been developed as part of the 'Guidance on Risk Assessment' under the Cartagena Protocol for Biosafety.

This meeting will address the concern that has been expressed by a number of participants (parties and nonparties) during the discussions on Risk Assessment and Risk Management, in the online forum and at MOPs 6 & 7, that the Guidance is not useful in its current form because it goes beyond what is commonly considered in actual cases of risk assessment. The purpose of this exercise is to develop recommendations for the guidance document based on a comparison of common experiences with multiple, actual cases of risk assessment.

PARTICIPANTS:

Participants from countries with experience based on approvals of multiple cases of risk assessment, and who have expressed concern over the usefulness of the roadmap, will participate in this discussion.

Currently, the following countries and tentative participants from each country include:

Argentina: ANBio
Australia: OGTR
Brazil: CTNBio (To be confirmed)
Canada: Sarah Davies / Phil Macdonald, CFIA
Columbia: Instituto Colombiano Agropecuario (To be confirmed)
European Union: EFSA (To be confirmed)
European Union: RIVM GMO Office
Japan: NITE (To be confirmed)
Mexico: CIBIOGEM
Paraguay: MAG (To be confirmed)
Philippines: DOST Biosafety Committee
South Africa: DEA / DAFF (To be confirmed)
USA: (USDA/APHIS)
USA: EPA (To be confirmed)

STEERING COMMITTEE:

, University of Minnesota, US (Chair)
USDA/FAS, US
, Estel Consult, UK
ILSI/CERA, US
, PRRI/Univ. Ghent/Univ. Brussels, Belgium
ABNE, Burkina Faso

METHOD:

In order to structure the discussion, participants are asked to complete an evaluation of the Roadmap based on a risk assessment case study of their choice, one that represents the most current process for risk assessment from their country.

To facilitate this evaluation, the following documents are attached:
1) The most recent draft of the Roadmap (Part I of the 'Guidance on Risk Assessment of Living Modified Organisms').
2) Table 1 which lists every point described in the roadmap, and a column at the end which can be filled in with an evaluation for each point as it is addressed (or not) in the case study.
3) Table 2 which includes four columns representing examples of evaluations of each point from the roadmap in Table 1, from risk assessments found on the BCH for Canada, Brazil, Argentina, and Japan of a specific case (MIR162 maize). The last column in Table 2 provides a summary of common elements across the four countries for each point of the Roadmap.

Participants will conduct this evaluation and provide their results to the meeting organizers 2 weeks before the meeting takes place. The meeting organizers will summarize this information to use as a focus for the discussion.

During the meeting, participants will present their individual evaluation, noting especially those points in the 'Roadmap' which were difficult to interpret as part of their risk assessment.

OUTCOMES:
The expected outcomes of this discussion will be:

1) a clear indication of where the Guidance (the Roadmap, specifically) reflects what is commonly found in 'actual cases' of risk assessments, and where it does not, or where this varies between cases
2) recommendations for how this information could be used to 'revise/improve' the Guidance
3) 'examples' from actual cases of risk assessment to support the recommendations.

Participants will agree on the best routes to disseminate these outcomes, possibly as a report to the Secretariat, and/or in a side-event at MOP8, and/or as a published manuscript.

MEETING DATE/LOCATION:
The proposed dates for the 2.5 day meeting are Feb 1-5, 2016

The meeting will take place in Washington DC.

Travel support is available for participants, as needed.
(*A competitive grant has been awarded by USDA/NIFA to University of Minnesota, in support of this meeting.)*

This conference is being organized by the Stakman Borlaug Center for Sustainable Plant Health of the University of Minnesota, with support from USDA National Institute for Food and Agriculture Biotechnology Risk Assessment Grant Program.

Sarah G. Davis - Re: Interview request from The Scientist magazine

From: Sarah G. Davis
To: Macdonald, Philip
Date: 2015-11-17 10:00 AM
Subject: Re: Interview request from The Scientist magazine

Yeah, it was kind of unclear at first but in a follow-up email to me, she was asking about our product-based system (and wanted us to compare it to the USDA's process-based one) so I flipped it to Martine.

>>> Philip Macdonald 2015-11-17 9:57 AM >>>
I tried to hand this to you because I think she was mostly interested in the science lens bit I'm sure Martine will be very capable.

It's the usual AHTEG experience burt there are some allies this time.

Cheers,
Phil

Sent from/Envoyé du BlackBerry.

>>> Sarah G. Davis 17/11/2015 8:34:01 AM >>>
Hey Phil,

So you know, I've let Martine know about this request and she'll likely field it. It seems to me that wants info. on our regulatory triggers. I hope Brazil is lovely!
S.

>>> Philip Macdonald 2015-11-13 4:11 PM >>>
Hello

I would be more than happy to provide an interview but I will be in Brazil participating in an ad hoc technical expert group on the risk assessment of LMOs. If you are looking for technical information on the risk assessment I or my colleagues in Science Branch can be of assistance. If you are looking for information on the regulation of GM crops, then you will need to contact my Program's colleagues for more information.

Best regards,

Philip Macdonald
(613) 773-5288
philip.macdonald@inspection.gc.ca | Facsimile / Télécopieur : (613) 773-5391
Director, Plant Health and Biotechnology Laboratory Services | Services de laboratoire pour la protection des végétaux et la biotechnologie , Canadian Food Inspection Agency | Agence canadienne d'inspection des aliments
1400 Merivale Rd. | 1400, chemin Merivale, Ottawa, ON K1A 0Y9
Government of Canada | Gouvernement du Canada
www.inspection.gc.ca
|

>>> 2015-11-13 3:23 PM >>>

Dear Mr. MacDonald,

I am writing an article for The Scientist about genetic engineering technologies that have led to deregulation of crops in the US. I'd like to learn more about the Canadian system of regulation and how this compares to the US's process-based review of new products.

Please let me know your availability for a phone interview next week. Thank you for your time and I look forward to speaking with you.

Best,

The Scientist
www.the-scientist.com

Skype:

From: "Colton, Brian" <Brian.Colton@nrc-cnrc.gc.ca>
To: "Bonfils, Anne-Christine" <Anne-Christine.Bonfils@nrc-cnrc.gc.ca>, 'Ross...
Date: 2015/11/20 9:42 AM
Subject: Editing the editor: CRISPR gets an "undo" button - Genome Alberta
Attachments: Nature Biotech SafequardingCRISPR-Cas9 gene drives in yeast Nov 2015.pdf

An interesting take and offering from Genome Alberta.

I've attached the Nature Biotech article referred in the article.

Enjoy,

B.

http://genomealberta.ca/blogs/editing-the-editor-crispr-gets-an-undo-button.aspx

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From:
To:
CC:

Date: 2015/11/23 4:31 PM
Subject: Re: SynBio - update
Attachments: Arabidopsis PsbS mutants (5).pdf

Hi

Thanks for joining this debate – you hit the nail on the head on many points:

Quick follow up:

1. Nulsegregants:

There are indeed no examples of a decision whether null segregants are covered by the EU regulations, because nobody ever asked for that. What Allen possibly referred to is the statement EFSA once made that it would not accept nullsegregants as a comparator, but that is a different question. What remains of course is how to establish what is a nullsegregant.

2. German opinion:

The quote from one of the German reports saying "The organisms produced by so-called new techniques fall under the scope of Annex I A Part 1 No. 1 of Directive 2001/18/EC" is indeed very straightforward, but incorrect. As you will see, the position of the German authorities is a different one.

3. Need to be specific

I very much endorse your comment that subsequent discussion would be helped by being more specific. In the past discussions, NBTs has been a basket of very different techniques, ranging from genome editing to grafting.

We have to be specific as to 1) what technique we are talking about and 2) which changes have been obtained by the use of those techniques. You are absolutely right that in the case of CRISPRs, they can be used for knock-outs, knock-ins, and allele replacement. In that context I look forward to your feedback on the attached info sheet we distributed for the workshop on 9 December.

Ciao

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On 22 November 2015 at 09:23, wrote:

> It would help to know if there have been specific examples of null
> segregants that have been regulated.
>
> Null segregants are in a bit of a limbo when it comes to the EU. EFSA
> prefers they not be used as comparators due to the possible presence of
> unintended effects, so as a minimum they are in a 'suspect' category.
> Nevertheless, I am pretty sure null segregants get imported to the EU in a
> lot meal produced by hybrid corn.
>
> As far as opinions go, the German one sounds pretty unequivocal to me:
> "The organisms produced by so-called new techniques fall under the scope of
> Annex I A Part 1 No. 1 of Directive 2001/18/EC." I have not had a chance
> to read the other opinions.
>
> Assuming the null segregant status does not become a stumbling block,
> subsequent discussion would be helped by being more specific.
>
> In the case of CRISPRs, they can be used for knock-outs, knock-ins, and
> allele replacement.
>
> Knockouts are for the most part indistinguishable from mutagenesis.
>
> Knock-ins will continue to be GMO under Cartagena and other places.
>
> What about allele replacement that can replace standard backcrossing in
> breeding programs? I think allele replacement can be the most useful of
> all the applications, and treating it as GMO would be a travesty.
>
>
>
>
>
> On 11/18/2015 4:59 AM, wrote:
>
> Hi
>
> Greetings from Malaysia.
>
> Apologies for this belated follow up – the last two weeks have been
> extremely busy with workshops in Ankara and in Selangor on reviewing
> biosafety systems.
>
> What I have noticed is that these questions are clearly a hot topic in
> many countries.
>
> One thing I would caution for is to suggest too easily that certain
> resulting organisms are regulated in certain regulatory systems.
>
> For example your claim that the EU has regulated null segregants is far
> from certain. I believe that null segregants are not covered by the GMO
> definition, and also that small point mutations produced through genome
> editing are not covered.
>

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> This is also the opinion of the authorities of Germany, UK, and Ireland in
> a letter to the European Commission.
>
> Yesterday, the Swedish Board of Agriculture has confirmed the
> interpretation that some plants in which the genome has been edited using
> the CRISPR-Cas9 technology do not fall under the European GMO definition.
> (see:
> http://www.upsc.se/about-upsc/news/4815-green-light-in-the-tunnel-swedish-board-of-agriculture-a-crispr-cas9-mutant-but-not-a-gmo.html
>).
>
> Cheers
>
>
>
>
>
> On 10 November 2015 at 08:15,
> wrote:
>
>> Hi,
>>
>>
>>
>> interesting conversation---but EU has regulated Case 1 and nulls. Case 1
>> has also been regulated in all other countries except in US when
>> Agrobacterium has not been used.
>>
>> FYI—there is an open comment period now for US regulations. International
>> and PRRI statement would be good. They are suggesting a risk assessment
>> model by characterizing crops and traits and regulatory trigger if one of
>> the 2 is considered risky. I spoke with lead on this last week—they
>> considered a trait as a genetic construct...we have long ways to go.
>>
>>
>>
>>
>>
>> *FR Notice:
>> https://www.federalregister.gov/articles/2015/10/06/2015-25325/clarifying-current-roles-and-responsibilities-described-in-the-coordinated-framework-for-the
>> <https://www.federalregister.gov/articles/2015/10/06/2015-25325/clarifying-current-roles-and-responsibilities-described-in-the-coordinated-framework-for-the>
>> *
>>
>> *OSTP Website:
>> https://www.whitehouse.gov/blog/2015/07/02/improving-transparency-and-ensuring-continued-safety-biotechnology
>> <https://www.whitehouse.gov/blog/2015/07/02/improving-transparency-and-ensuring-continued-safety-biotechnology>
>> *
>>
>> *OSTP Interagency Memo (2 July 2015):
>>
https://www.whitehouse.gov/sites/default/files/microsites/ostp/modernizing_the_reg_system_for_biotech_products_memo_final.pdf

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>>
<https://www.whitehouse.gov/sites/default/files/microsites/ostp/modernizing_the_reg_system_for_biotech_products_memo_final.pdf>
>> *
>>
>>
>>
>> best,
>>
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>>
>> *From:*
>> *Sent:* Monday, November 9, 2015 2:05 PM
>> *To:*
>> *Cc:*
>>
>>
>>
>>
>>
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>>
>>
>>
>>
>>
>>
>>
>>
>> *Subject:* Re: SynBio - update
>>
>>
>>
>> Hi
>>
>>
>>
>> Thanks - and now it is my turn to apologise for the delayed response.
>>
>>
>>
>> You make an important distinction, i.e. what the definition actually says
>> and how it might be interpreted by (some) authorities.
>>
>>
>>
>> Before addressing your questions: first some words of caution about
>> terminology.
>>
>> 1) The term 'transgenesis' is not used in any of the definitions. Please
>> avoid using terms that are not used in the definitions.
>>
>> 2) make a distinction between 'not covered' and 'should be exempted'.
>>
>>

Philip Macdonald;

>>
>> Turning to your 2 cases:
>>
>> Case 1: organism produced by modern biotechnology where a native gene is
>> introduced from one crossable variety to another (I assume you refer to a
>> case whereby only native genes are transferred and not also foreign DNA as
>> selection markers).
>>
>> Case 2: an organism produced by chemical or radiation mutagenesis that
>> expresses a novel trait.
>>
>>
>>
>> Looking at the definitions, I would conclude for these cases:
>>
>>
>>
>> Under CPB:
>>
>> Case 1: not a GMO, because the obtained genetic combination is not novel
>> in the sense that it does not overcome natural physiological reproductive
>> or recombination barriers.
>>
>> Case 2: not a GMO, because the technique used is not a technique of
>> modern biotechnology.
>>
>>
>>
>> Under EU:
>>
>> Case 1: not a GMO, because the obtained genetic combination can occur
>> naturally by mating or recombination
>>
>> Case 2: Exempted from the Directive.
>>
>>
>>
>> Remember, the requirements of 1) the technique and 2) the novelty are
>> cumulative, i.e. if one of the two is absent, then not a GMO/LMO. For that
>> same reason, I would say that null segregants, small deletions or point
>> mutations do not constitute a GMO/LMO.
>>
>>
>>
>> The danger of assuming that the authorities will apply a process based
>> interpretation, and repeating that assumption frequently, is that it
>> confirms those authorities who incorrectly think that the definition is in
>> fact process based.
>>
>>
>>
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>>
>> Ciao!
>>
>>

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>> On 26 October 2015 at 19:31,
>> wrote:
>>
>>
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>>
>>
>> Just now taking some time to digest what you wrote here regarding the
>> definition of GMO/LMO and new breeding techniques, so my commentary here is
>> intended more to improve my understanding than to take a position. While
>> the definition of GMO/LMO seems in principle to be based on process *and*
>> novelty, I would be interested to know how the CPB and the EU would deal
>> with these two cases in practice: 1) an organism produced by transgenesis
>> but expressing a non-novel trait (e.g. a transgenic plant where a native
>> gene is introduced from one variety to another because it would be more
>> rapid than breeding), or 2) an organism produced by chemical or radiation
>> mutagenesis that expresses a novel trait.
>>
>>
>>
>> Relating to the CPB definition, case 1 possesses a non-novel combination
>> of genetic material even though it is obtained through the use of modern
>> biotechnology. Case 2 possesses a novel combination, but not through
>> modern biotechnology. I would assume case 1 would be treated as an LMO,
>> but case 2 would not? If that is the case, then process trumps novelty in
>> the definition. So if gene editing techniques were employed to produce
>> case 1, would case 1 still be an LMO, because it is captured by the "modern
>> biotechnology" element? If so, then process would trump novelty again.
>>
>>
>>
>> Relating to the EU definition, case 1 is an organism in which the
>> genetic material has *no*t been altered in a way that does not occur
>> naturally by mating and/or natural recombination (I'm actually now having
>> trouble parsing our this definition). Case 2 has been altered by a process
>> that results in a combination that does *not* occur naturally by mating
>> and/or natural recombination. I would assume however that in the EU, case
>> 1 would still be treated as a GMO, while case 2 would not? Likewise
>> process trumps novelty in both cases. To me the hope that is offered by
>> the EU definition is that one can argue the process of gene editing makes
>> use of natural recombination processes (non-homologous end-joining and
>> repair, for example) and therefore could be used to exempt both cases from
>> the GMO definition.
>>
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>> On Sat, Oct 24, 2015 at 9:57 AM,
>>
>>
>> Dear All,
>>
>> I follow up on our communications about the Synthetic Biology discussions
>> under the CBD.
>>
>> Quick update and request for feedback:
>>
>> *AHTEG SYNBIO *
>>
>> The first AHTEG on SynBio took place from 21 to 25 September in
>> Montreal. Several people on this email list participated in that AHTEG.
>>
>> The feedback shows that this process was an eye-opener for many, at times
>> frustrating for some, but that nevertheless the resulting report is found
>> to be fairly balanced in that it reflects the various views on the topics:
>>
>> - Relationship between synthetic biology and biological diversity;
>>
>> - Similarities and differences between LMOs and SynBio
>>
>> - Adequacy of existing regulatory instruments to address SynBio;
>>
>> - Operational definition of synthetic biology;
>>
>> - Potential benefits and risks to the conservation and sustainable use of
>> biodiversity
>>
>> - Best practices on risk assessment and monitoring;
>>
>>
>>
>> We will inform you when the final report is posted on the CBD site. The
>> report of the AHTEG will be submitted to the SBSTTA (see below).
>>
>> As the AHTEG documents and discussion show, there are many links to
>> topics under the Cartagena Protocol, e.g.:
>>
>> - definitions
>>
>> - Environmental Risk Assessment
>>
>> - Socio – Economic considerations
>>
>>
>>
>> As regards definitions, I draw your attention to a discussion we have in
>> Europe on the definition of a GMO in relation to New Breeding Techniques. I
>> attach below for your information an email exchange with my colleagues in
>> Europe. Main message is that while the definitions of GMO and LMO refer to

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>> certain techniques, the decisive element in those definitions is whether
>> the resulting organisms possess novel genetic combinations, i.e. genetic
>> combinations that "do not occur naturally by mating or recombination" (as
>> phrased in the EU) or "overcome natural physiological reproductive or
>> recombination barriers" (as phrased in the CPB). In short, these
>> regulations are not 'process based', because both the use of the technique
>> and the novelty of the resulting genetic combinations are relevant. This
>> discussion will also be relevant for SynBio.
>>
>> As to Environmental Risk Assessment and Socio–Economic considerations, we
>> have similar informal discussion groups on those CPB topics and will keep
>> you posted of relevant developments there.
>>
>>
>>
>>
>>
>> *SBTTA *
>>
>> The result of the on line discussion and the report of the AHTEG will be
>> submitted to the Subsidiary Body on Scientific, Technical and Technological
>> Advice. The first upcoming meeting of the SBSTTA is SBSTA-19 from 2 - 5
>> November 2015, Montreal. The next SBSTTA will be from 25 - 29 April 2016
>> in Montreal.
>>
>> The topic is included on the agenda of SBSTTA-20, in April 2016. (see:
>> https://www.cbd.int/doc/?meeting=SBSTTA-20).
>>
>> It will be very good if some of us who participated in the on line
>> discussions and/orteh AHTEG can participate.
>>
>>
>>
>> *COP13 *
>>
>> The COP13 will be held from 4 - 17 December 2016, in Cancun.
>>
>> (See: https://www.cbd.int/doc/?meeting=COP-13).
>>
>>
>>
>> As discussed, in addition to being prepared for the negotiations, it will
>> be good to hold a side event on SynBio during COP13, preferably including
>> young students (e.g. the iGEM initiative). and
>> have already indicated to be willing to help with that. We will keep you
>> posted on that.
>>
>>
>>
>> Wishing you all a great remainder of the weekend !
>>
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>>

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>>
>>
>> Dear All,
>>
>> Many thanks for your responses to my emails about the EU/CPB definitions
>> of GMO/LMO, and the implications for organisms developed by New Breeding
>> Techniques (NBTs).
>>
>> As several more people have been added to this list, let me briefly
>> summarise:
>>
>> While these definitions refer to certain techniques, the decisive element
>> in those definitions is whether the resulting organisms possess novel
>> genetic combinations, i.e. genetic combinations that "do not occur
>> naturally by mating or recombination" (as phrased in the EU) or "overcome
>> natural physiological reproductive or recombination barriers" (as phrased
>> in the CPB).
>>
>> In short, these regulations are not 'process based', but rather both the
>> use of the technique *and* the novelty of the resulting genetic
>> combinations are relevant.
>>
>> This is concisely reflected in the CPB definition: "an LMO is a living
>> organism that 1) possesses a novel combination of genetic material 2)
>> obtained through the use of modern biotechnology".
>>
>> In the EU definition this phrased a bit more opaquely with "*an organism
>> in which the genetic material has been altered in a way that does not occur
>> naturally by mating and/or natural recombination*". Over the years there
>> has been some discussion as to whether "altered in way" refers to the
>> technique, to the end result, or to both. As I illustrated in my previous
>> emails, the definition and the annexes that belong to that definition shows
>> that this "altered in a way" refers to both the technique used and the
>> novelty of the genetic combination obtained.
>>
>> This interpretation is nothing surprising, because this notion of
>> 'novelty' has been the consistent element since the first definitions in
>> the mid-80s, and (as the European Commission has stated) the EU GMO
>> definition is consistent with the definition of the CPB.
>>
>> Some of you have expressed concern that nevertheless the EC may follow a
>> purely 'process based' interpretation. That seems unlikely, if you see for
>> example what Commissioner Borg said in reply to questions from MEPs: " .....
>> the definition of GMO in the EU legislation is referring both to the
>> characteristics of the organism obtained and to the techniques used....". See
>> link
>> <http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-%2f%2fEP%2f%2fTEXT%2bWQ%2bE-2014-006525%2b0%2bDOC%2bXML%2bV0%2f%2fEN&language=EN>.
>> In addition, several EU Competent Authorities have written to the EC that
>> they are of the view that the EU definition of a GMO relies *both* on
>> the process used and the resulting organism/product.
>>
>> Last but not least, your responses confirm that most – if not all – of
>> you endorse the view that a purely technique based interpretation would
>> make little sense.

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>>
>> What our email-exchanges have also taught us is that it is important to
>> make clear whether we are expressing what we think the definition says, or
>> whether we express what we think others believe what the definition says.
>>
>> Turning to organisms produced through NBTs: as said, for a meaningful
>> discussion it is important to make clear to which NBTs we are referring,
>> because genome editing techniques are for example very different from DNA
>> methylation techniques, again different from Agroinfiltration, etc. etc.
>>
>> As regards the question to what extent organisms produced through
>> specific NBTs fall under the GMO/LMO definition: the answer to that
>> question depends on whether these techniques have resulted in novel genetic
>> combinations, i.e. combinations that go beyond natural mating or
>> recombination / natural physiological reproductive or recombination barriers
>>
>> Such a nuanced approach is also reflected in the report of the WGNT,
>> which for example for the ZFN technique made a distinction in FSN1, FSN2
>> and FSN 3, based on the extent of the alteration.
>>
>> See also the attached letter of EFSA to the European Commission of 15
>> October 2015. While I believe that some details in that letter would need
>> some further discussion, the overall approach confirms the notion that when
>> talking about definitions the resulting organisms need to be taken into
>> account. What I also find very important in the EFSA letter is the
>> statement that we should remain aware that this field evolves rapidly. I
>> fully endorse the notion that we should keep monitoring future
>> developments, and I believe that in doing so we should look beyond NBTs,
>> and also look at areas as Synthetic Biology (see some articles below this
>> email), e.g. what about XNA?
>>
>> As discussed, with the rapid development of new techniques and with the
>> increasing knowledge of genomic variability, the challenging task is of
>> course to fine tune the grey areas, which would be a great topic for a
>> scientific brainstorm workshop to discuss 'how novel is novel' and related
>> topics.
>>
>> We have received many enthusiastic reactions to the idea of holding such
>> a workshop, and a few of you have already prepared the attached draft
>> info-sheet for CRISPR, that can be used in the discussions. Please keep
>> that draft info-sheet to yourselves for now.
>>
>> We have fixed the workshop on 9 December, at the Free University of
>> Brussels. Program and details will follow.
>>
>> Please send me at the latest on 5 November your interest in participation
>> (repeated request: please do not copy everyone to avoid clogging of
>> inboxes). For those who cannot cover their travel from their own budgets,
>> we have secured some extra travel funds with the help of
>>
>> Looking forward to hearing from you
>>
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>>

s.19(1)

>> PS: Below some recent articles on NBTs.
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>>
>>
>> Faculty of Sciences, Faculty of Law, Ghent University, Belgium
>>
>> Faculty of Science and Bio-Engineering Sciences, Free University
>> Brussels (VUB
>> <https://caliweb.cumulus.vub.ac.be/caliweb/?page=course-offer&id=008938&anchor=1&target=pr&year=1415&language=en&output=html>),
>> Belgium
>>
>> c/o International Plant Biotechnology Outreach (IPBO)
>> <http://ipbo.vib-ugent.be/team/ IIC/UGent
>>
>> Technologiepark 3, B-9052 Gent-Zwijnaarde, Belgium
>>
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>> The Economist | Gene editing: Even CRISPR:
>> http://www.economist.com/news/science-and-technology/21668031-scientists-have-found-yet-another-way-edit-genomes-suggesting-such-technology-will?frsc=dg%7Ca
>>
>>
>>
>> *Wired** covers Monday's National Academy of Sciences meeting on human
>> genome editing*
>>
>> *Wired:* Science Would Like Some Rules for Genome Editing, Please
>> <http://www.wired.com/2015/10/science-like-rules-genome-editing-please/>
>>
>>
>>
>> *Science:* Four synthetic biology inventions that flummox the feds
>> <http://news.sciencemag.org/scientific-community/2015/10/four-synthetic-biology-inventions-flummox-feds?utm_campaign=email-news-weekly&et_rid=35367769&et_cid=51999>
>>
>> *Wilson Center:* The DNA of the U.S. Regulatory System: Are We Getting
>> It Right for Synthetic Biology?
>> <http://www.synbioproject.org/publications/dna-of-the-u.s-regulatory-system/>
>>
>> *Bloomberg View:* This Is No Way to Regulate GMOs
>> <http://www.bloombergview.com/articles/2015-10-21/this-is-no-way-to-regulate-genetic-modification>
>>
>> *Nature* (news): CRISPR tweak may help gene-edited crops bypass
>> biosafety regulation
>> <http://www.nature.com/news/crispr-tweak-may-help-gene-edited-crops-bypass-biosafety-regulation-1.18590>
>>
>> *Nature Biotechnology:* DNA-free genome editing in plants with
>> preassembled CRISPR-Cas9 ribonucleoproteins
>> <http://www.nature.com/nbt/journal/vaop/ncurrent/full/nbt.3389.html>

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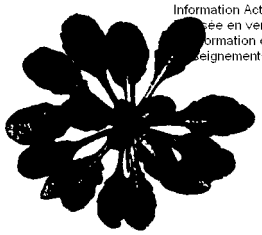
The *Arabidopsis thaliana* PsbS mutant

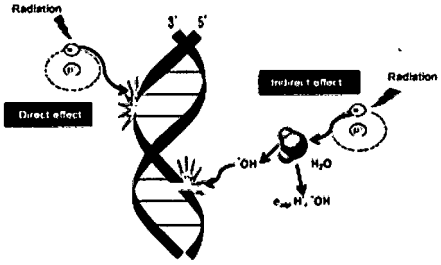
The same mutant produced five times, but which ones are within the scope of the European GMO legislation?

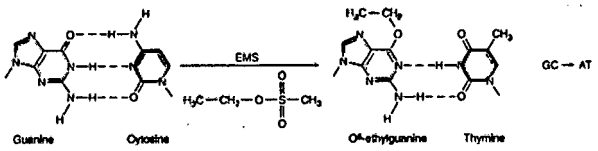


What is the function of PsbS?
PsbS is a protein which is involved in photosynthetic light harvesting and has been characterized as a 'safety valve'. Plants that lack the protein show reduced fitness and seed production under natural conditions. Mutant plants that fully lack the protein or produce a dysfunctional protein have been obtained in different ways.

A. The radiation mutant

The first PsbS mutant was made by exposing Arabidopsis plants to fast neutrons. The fast neutrons generate damage in the DNA that is repaired by the cells own DNA-repair machinery. During this repair, the whole PsbS gene was deleted and PsbS is therefore not present in the plant. However changes in other genes may also have occured following the radiation.



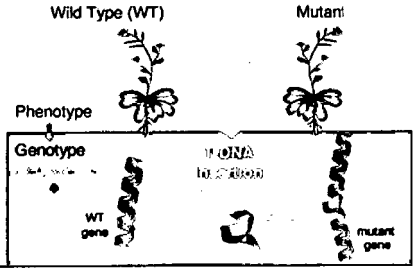


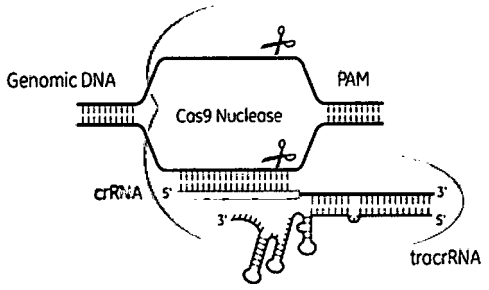
B. The chemically induced mutant

The second PsbS mutant was made by exposing Arabidopsis plants to the chemical mutagen EMS. One letter in the gene for PsbS was changed leading to a dysfunctional PsbS protein.

C. The T-DNA mutant

The third PsbS mutant was made by transferring so-called T-DNA from the soil bacterium *Agrobacterium tumefaciens* to Arabidopsis plants. The T-DNA has inserted into the PsbS gene leading to a disruption of the gene. The result is that the PsbS gene is no longer functional.





D. & E. The modern genome edited mutant

The most recent technology to generate PsbS mutants is the so-called CRISPR/Cas mediated genome editing. This CRISPR/Cas system generates two double strand breaks close to each other at predetermined locations in the PsbS gene. The DNA-repair machinery repairs the break, deleting the DNA between the breaks leading to a dysfunctional PsbS gene. The intermediate mutant that still contains the DNA for producing the CRISPR/Cas complex that generates the double strand break is called mutant D. The final mutant E is produced from mutant D after a round of spontaneous fertilization. One quarter of the offspring no longer contains the genes for the complex and these are selected a mutant E. They contain no foreign DNA and only differ from wild type Arabidopsis by a small deletion in the PsbS gene.

A GMO or not a GMO?

Mutants A and B are not within the scope of the European GMO legislation. Mutant C is, even though T-DNA sequences are shown to naturally occur in crops like tobacco and sweet potato, considered a GMO. But what about mutant D and E? Mutant D still contains foreign DNA and is therefore considered a GMO. Mutant E does not contain foreign DNA and only lacks a number of DNA base pairs in the PsbS gene. Does this removal of a few base pairs constitute a novel combination of genetic material? Probably not. When compared to the mutants A and B it would be illogical to subject the genome edited mutant E to the requirements of the GMO legislation.

Philip Macdonald - CRISPR Congress: Join the on-going revolution

From:
To: "P Macdonald" <philip.macdonald@inspection.gc.ca>
Date: 2015/12/15 6:18 PM
Subject: CRISPR Congress: Join the on-going revolution

Optimize your CRISPR Design to Efficiently Power Novel Applications

The wait is finally over for the CRISPR gene editing community who will be reuniting at the **2nd Annual CRISPR Congress** (February 23-25, Boston).

For the first look at the newly launched brochure and unrivalled speaker line up - **download the program here**.

With the superior applications of CRISPR gaining momentum, **CRISPR Congress 2016** pioneers the translation of CRISPR technology into **clinically effective CRISPR-based therapies**.

Below is a snapshot of the 25 expert speakers who will be delivering **case studies** of how they are developing and optimizing the technology to improve the application of CRISPR/Cas9:

- **Emmanuelle Charpentier**, Professor, Max Planck Institution for Infection Biology, MIMS, Umeå University
- **George Church**, Professor of Genetics, Harvard Medical School
- **Alexandra Glucksmann**, Chief Operating Officer, Editas Medicine
- **Lorenz Mayr**, VP Reagents & Assay Development, AstraZeneca
- **Rodger Novak**, Chief Executive Officer, CRISPR Therapeutics
- **Rachel Haurwitz**, President & CEO, Caribou Biosciences
- **Jon Moore**, CSO, Horizon Discovery

Download the brochure for the full speaker line-up.

What is new for 2016?

- Enhance the delivery and efficiency of **CRISPR/Cas9 in primary cells**
- Engineer the next generation of **humanized animal models & cell lines** for advanced target identification and drug discovery
- Develop strategies to perform **large scale genome wide screening** for the development of CRISPR libraries
- Learn how to independently design and optimize **novel emerging CRISPR enzymes (including Cpf1)** to enhance specificity and efficiency
- Understand the **regulatory requirements** for CRISPR/Cas9-based therapeutic development

Join us in February to keep pushing the boundaries of what is possible for precision genome engineering.

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You have received this e-mail in the genuine belief that its contents would be of interest to you. To not receive these messages from Scientific Direct or other carefully selected organizations, please go to our preference page.

Scientific Direct
1500 Spring Garden Street
4th Fl
Philadelphia, PA 19130
USA

From: Dylan Levac
To: Andrea Hitchon; Cecile Girard; Philip Macdonald; Sarah G. Davis
Date: 2016/01/14 11:31 AM
Subject: DIY Home CRISPR kit funded online

Hi everyone,

Thought this might be of interest. A crowd funding campaign was started to engineer CRISPR/Cas9 protocols, and kits that can be successfully executed in your home. To date it has received $49K USD or, based on the exchange rate, $70.5K Canadian ='(

Information can be found at the following link.

https://www.indiegogo.com/projects/diy-crispr-kits-learn-modern-science-by-doing#/

Best wishes,
Dylan

s.19(1)

From:
To:
CC:
Date: 2016/02/03 2:00 PM
Subject: Re: FW: CBD Notification 2015-139 – Peer review of the outcomes of the process in response to decision XII/24 on synthetic biology

Thanks for this, and apologies for just now getting around to reading it. My own thinking aligns well with the comments in this document, and I particularly like arguments against defining the term "synthetic biology" altogether.

On Sat, Jan 30, 2016 at 11:22 AM, wrote:

> Dear All,
>
>
>
> has suggested that I send you a copy of the attached submission to
> CBD consultation from the UK SBLC. Apologies to those of you who will
> thereby get this email more than once.
>
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>
> Yours,
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>
>
> University of Edinburgh,
>
> Old Surgeons Hall, High School Yards,
>
> Edinburgh EH1 1LZ
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>
> 07545 641 773
>
> www.innogen.ac.uk
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>
> *From:*
> *Sent:* 30 January 2016 15:31
> *To:* 'synbio@cbd.int' <synbio@cbd.int>
> *Cc:*
>
>
>

s.19(1)

>
>
> >
> *Subject:* CBD Notification 2015-139 – Peer review of the outcomes of the
> process in response to decision XII/24 on synthetic biology
>
>
>
> Dear
>
>
>
> Please find attached a response to your request as
> Secretariat of the Convention on Biological Diversity, for comments on
> (a) Updated report and synthesis of views in response to
> paragraph 7(b) of decision XII/24; and
>
> (b) Report of the meeting of the Ad Hoc Technical Expert Group
> on Synthetic Biology.
>
>
>
> The UK Synthetic Biology Leadership Council was invited to send this
> response by the UK Department of Environment, Food and Rural Affairs
> (DEFRA).
>
>
>
> I would be grateful if you would acknowledge receipt of our submission.
>
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> Yours sincerely,
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>
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> University of Edinburgh,
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> Old Surgeons Hall, High School Yards,
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> Edinburgh EH1 1LZ
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> 07545 641 773
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> www.innogen.ac.uk
>
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>
> The University of Edinburgh is a charitable body, registered in
> Scotland, with registration number SC005336.
>
>

s.19(1)

From:
To:
CC:
Date: 2016/02/19 9:12 AM
Subject: Re: NL report on gene drive

Thanks for this,

I would be interested to know more details if they are available, regarding the reasoning behind the conclusion that the current risk assessment method is inadequate.

I think we should start compiling a list of similar decisions be regulatory agencies, so if anyone else on this list is aware of similar decisions, please append to this thread.

I think these would be a good start to have on the PRRI password accessible site.

On Fri, Feb 19, 2016 at 8:45 AM,
wrote:

> Dear all,
>
> Just to inform you that recently our GMO Office published a policy report
> on gene drive and its possible consequences for risk assessment.
> Although this report is written for the European situation and for
> contained us of GMOs, it might still be of interest for you.
>
> The report is available in English and is attached to this mal.
>
> You can also follow the link to our website:
>
>
http://www.rivm.nl/en/Documents_and_publications/Common_and_Present/Newsmessages/2016/Need_for_adjustment_authorisation_for_gene_drive_applications
>
> Kind regards,
>
>
>
>
> GMO Office
> RIVM/VSP
> PO Box 1 3720 BA Bilthoven
> The Netherlands
>
> Phone number: · or +
>
>
>
> * Proclaimer RIVM http://www.rivm.nl/Proclaimer*
> <http://www.rivm.nl/Proclaimer>

s.19(1)

From:
To: "philip.macdonald@inspection.gc.ca" <philip.macdonald@inspection.gc.ca>
Date: 2016/03/22 2:18 PM
Subject: Chapter 5
Attachments: Macdonald revised djm AA JM.doc; revised JM.docx

Hi Phil

Many thanks for submitting you interesting Chapter for the biosafety book.

Please find attached an annotated version which has been reviewed by all three editors so there are quite a few comments/suggestions, most pretty minor and some dealing with formatting issues for the publisher.

I also attach my own chapter which covers gene editing technologies that may be relevant to cross reference and also for formatting guidance.

We would greatly appreciate it if you could get this back to us in the next 3 weeks. Meanwhile if you have any queries please let us know.

best wishes

University of South Wales, CF37 4AT, United Kingdom
Google Scholar outputs: http://scholar.google.co.uk/citations?hl=en&user=GQc6wQsu-BkC

Tel:
Email:

Pages 725 to / à 739

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sont retenues en vertu des articles

18(c), 20(1)(d), 19(1)

of the Access to Information

de la Loi sur l'accŠs … l'information

Pages 740 to / à 750

are withheld pursuant to sections

sont retenues en vertu des articles

18(c), 20(1)(d)

of the Access to Information

de la Loi sur l'accŠs … l'information

From: Luc Bourbonniere <Luc.Bourbonniere@hc-sc.gc.ca>
To: Jordan Bean <jordan.bean@hc-sc.gc.ca>, Neil Strand <neil.strand@hc-sc.gc...
Date: 2016/03/17 6:03 PM
Subject: CRISPR Is Going To Revolutionize Our Food System—And Start A New War Over GMOs

http://www.fastcoexist.com/3056693/crispr-is-going-to-revolutionize-our-food-system-and-start-a-new-war-over-gmos

s.19(1)

From: Cheryl Dollard
To: Ameen, Abdullahi; Castro, Karen; Corbett, Cheryl; Cumming, Heather; ...
CC: Mahran, Amro; Niederberger, Thomas; Ross, Pamela; Sabourin, Marc
Date: 2016/03/18 8:17 AM
Subject: Re: DIY Bio Summit - Mini Report

Thanks Andrea and Dylan -
This is a great initiative.
I have copied our Plant Lab Directors, in case they would like to share this information with their staff.
I look forward to the final report as well!

Kind regards
Cheryl D.

>>> Christine Tibelius 2016-03-17 4:20 PM >>>
Thank you Andrea. This sounds very interesting, particularly the fact that this community may not be overly aware of Canada's regulatory frameworks and some of the challenges that may be faced. I would be curious to know how other countries are handling this. Please loop me in when the PHAC report comes out.

Christine

Sent from/Envoyé du BlackBerry.

>>> Andrea Hitchon 17/03/2016 4:06:54 PM >>>

Hi all,
Yesterday Dylan and I had the opportunity to attend the 'Canadian do-it-yourself biology summit' hosted by the Public Health Agency (PHAC). I thought some of you might be interested in hearing about the summit and following future developments. The purpose of this event was to increase collaboration between government agencies and community labs, especially as it relates to safety regulations. Community 'DIY' labs are places where diverse thinkers, who may not have a science background, can access lab equipment and carry out experiments. Generally, funding is crowdfunded and users pay a lab membership fee. Many projects discussed focussed on understanding the science behind DNA cutting, DNA fingerprinting, synthetic biology, CRISPR, biosensors, fermentation, mycology, and DNA barcoding. Spaces may also 'incubate' small businesses. Background of the event and DIY Biology community in Canada can be found here: http://www.canadianbusiness.com/business-news/ottawa-galvanizes-citizen-science-with-do-it-yourself-biology-summit/.
A goal of many of these labs is science education and public engagement. Currently, many are offering workshops addressing public perception towards genetic modification. While the focus of this summit was on ensuring these groups foster a culture of safety, following CFIA import/export regulations was briefly discussed. There is also interest in moving from level one containment lab spaces, to level two. As technology continues to advance, and prices drop – the capabilities of DIY Bio spaces will greatly increase. Currently, DIY BIO Toronto has a Nanopore MinION - one of the most advanced Next Generation Sequencing platforms. The same group also just bought a mass spectrometer. A sentiment expressed by external stakeholders was that Canadian regulators as a whole were behind others including Great Britain, the EU, and the US in considering the biosafety, biosecurity, and unique regulations and communications that may be required to adequately manage the risk that DIY Bio may pose without stifling innovation.
PHAC will be preparing a final report, I would be happy to forward this to anyone interested once I receive it.
Andrea
P.S. Keep your eyes open if you are interested in joining the DIY movement – is working to start-up DIY BIO Ottawa!

Andrea Hitchon

Risk Assessor - Biotechnology, Plant and Biotechnology Risk Assessment Unit
Canadian Food Inspection Agency / Government of Canada
Andrea.Hitchon@inspection.gc.ca / Tel: 613-773-6332

Évaluatrice des risques - biotechnologie, Unité d'évaluation des risques des végétaux et des produits de la biotechnologie
Agence canadienne d'inspection des aliments / Gouvernement du Canada
Andrea.Hitchon@inspection.gc.ca / Tél: 613-773-6332

From: Christine Tibelius
Sent: 2016-04-01 1:27:26 PM
To: Philip.Macdonald@inspection.gc.ca
CC: Sarah.Davis@inspection.gc.ca;Cameron.Duff@inspection.gc.ca;Dylan.Levac@inspection.gc.ca
BCC:
Subject: Fwd: Interview re: synthetic biology regulatory "gap" analysis

Hi Phil,

Just to follow up on this, Sarah, Dylan and I are planning to meet, go over the questions and provide a Directorate level response. The appointment isn't set yet but you are welcome to join us and provide your expertise.

Christine

>>> > 2016/03/31 3:37 PM >>>
Dear Ms Tibelius,

I spoke with recently and he suggested that I contact you on the matter below.

I was retained to carry out **a gap analysis on the regulation of synthetic biology within the federal Health Portfolio.**

This consulting work has been commissioned by Andrew Atkinson, HC Science Policy Directorate (copied here) and Kathrina Yambao (PHAC). While they have been involved in the selection of the interviewees and development of questions, I remain responsible for the selections made.

I would like to book an appointment with you to discuss the questions shown below ("Appendix") for approximately 30-60 minutes. You have the choice between an in-person or phone interview. The questions below are only starting points and you will have some freedom to express your views.

Your input will feed into a priority setting and solution seeking workshop (tentatively planned for May 2016) and a final report. As an interviewee, you will be invited to the workshop. The report is destined for distribution to regulators within the Health Portfolio. We will provide you with a copy of the report once it is completed.

We plan to acknowledge your participation in the report but we can also keep your name anonymous if you prefer. We will, however, disclose that someone in your Directorate was interviewed. Furthermore, your participation is voluntary and you may back out of your involvement at any time without explaining why.

Please let me know if you can make yourself available for this interview (or if you have any questions or concerns) – it would be much appreciated!

Please note that I have also contacted Phililp MacDonald and Sarah Davis on this matter.

(My current resume, FYI, is attached here)

With best regards,

www.linkedin.com/in

Appendix: Questions (prompts) for semi-structured interviews:

When answering the questions below, please choose a broad, encompassing concept of synthetic biology. It is more important to be inclusive than, say, legalistic at this stage. If would you like to have a starting point, please consider this definition:

"Synthetic biology is an emerging area of research that can broadly be described as the design and construction of novel artificial biological pathways, organisms or devices, or the redesign of existing natural biological systems." (from the UK Royal Society)

1. Would you like to remain anonymous?

2. Do we have the permission to record the interview for the purpose of transcription and analysis?

3. Setting aside the above UK definition, how would you define (or scope) synthetic biology?

4. Do you follow current trends in synthetic biology? In particular, are you aware of robotic operations that produce tens of thousands of variants per month (with the implication of potentially large numbers of regulatory notifications)

5. Given the direction of synthetic biology, where do you envision the greatest challenges or gaps your regulatory domain? (please explain if you do NOT see any challenges or gaps)

6. Are you aware of important regulatory challenges or gaps outside your domain, but within the GoC Health Portfolio?

7. Which synthetic biology processes and products are the most challenging to your regulatory practice? (These can be products already on the market or in the research pipeline).

8. Are the existing and expected gaps in the domains of (a) laws, regulations, standards or guidelines, (b) structures and coordination, (c) expertise and capacity? Please specify.

9. Are you aware of any existing or expected challenges that you would consider "game-changers" or "paradigm-shifters"? Please specify.

10. For the gaps that you would select as top priorities, do you have ideas for solutions?

11. What are some of the key strengths within your regulatory domain?


TEXT.htm


(2015-11) Resume.pd

12. Is there anything you would like to add or emphasize?

From: PSS-SSV Plant Science Scan/Survol Science des Végétaux
To: PSS-SSV Plant Science Scan/Survol Science des Végétaux
Date: 2016/04/05 8:20 AM
Subject: Plant Science Scan/Survol science des végétaux
Attachments: CFIA_ACIA_-_#7927043_-_vR_-_Plant_Science_Scan_Edition_15_April_2016.DOC.DRF; CFIA_ACIA_-_#7926973_-_vR_-_Survol_des_végétaux_édition_15_avril_2016.DOC.DRF; Plant Science Scan Edition 15 April 2016.pdf; Survol science des vegetaux edition 15 avril 2016.pdf

The Plant Science Scan is a compilation of publicly available information on issues of potential regulatory significance to the CFIA's Plant program. It provides readers with a brief summary and references for recently released information on regulated and emerging plant pests and diseases, invasive plant species and issues relating to Plants with Novel Traits (PNTs) and biotechnology.

In previous years similar Plant program related information has been distributed via the "Science Scan", "Science Intelligence Reports" and the "Plant Health Early Warning System" (PHEWS). As in the past, the Plant Science Scan is intended to be informational, communicating emerging scientific and technical information relevant to the CFIA's Plant program.

Receipt of this email indicates that you are currently subscribed to receive the electronically circulated Plant Science Scan. Should you wish to be removed from this Plant Science Scan distribution list, or should you be receiving this as a forwarded email and wish to be added to the distribution list, please send an email indicating your preference to PSS-SSV@inspection.gc.ca

Le Survol - science des végétaux est une compilation de renseignements publics sur des dossiers pouvant avoir de l'importance au chapitre de la réglementation pour le programme des végétaux de l'ACIA. Il fournit aux lecteurs un résumé des renseignements récents sur les maladies et les phytoravageurs réglementés et émergents ainsi que sur les espèces végétales envahissantes, en plus des références connexes. Le Survol traite également des végétaux à caractères nouveaux (VCN) et de la biotechnologie.

Au cours des années précédentes, des renseignements similaires sur le programme des végétaux ont été diffusés par l'entremise du 'Compte Rendue Scientifique', du 'Science Intelligence Reports' et du 'Plant Health Early Warning System' (PHEWS). Comme dans le passé, le Survol - science des végétaux est préparé à titre informatif et vise à communiquer de nouveaux renseignements scientifiques et techniques pertinents quant au programme des végétaux de l'ACIA.

Si vous avez reçu le présent courriel, cela signifie que vous figurez sur la liste des personnes qui reçoivent par voie électronique le Survol - science des végétaux. Si vous souhaitez retirer votre nom de la liste de distribution ou si, au contraire, ce courriel vous est transféré et que vous souhaitez ajouter votre nom à la liste de distribution, veuillez envoyer un courriel à l'adresse PSS-SSV@inspection.gc.ca en indiquant votre préférence.

Brittany Day
Plant Research & Strategies

Canadian Food Inspection Agency
1400 Merivale Rd. Tower 1
Ottawa, ON, K1A 0Y9

Brittany.Day@inspection.gc.ca / Tel: 613-773-5525

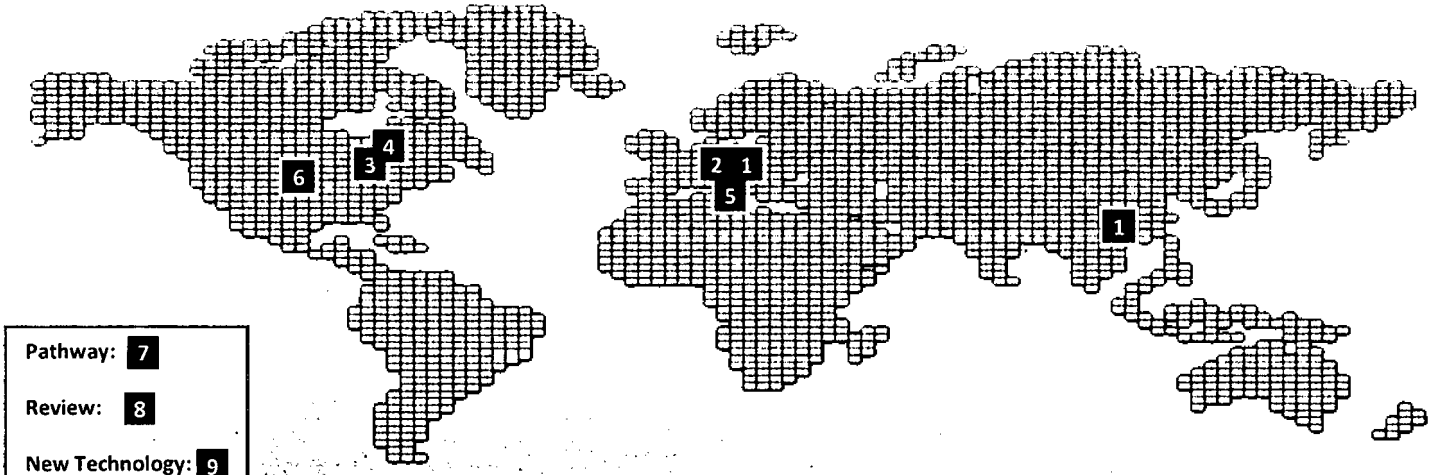
PLANT SCIENCE

ISSN 2369-4254

Edition 15, April 2016

BACKGROUND: The Plant Health Science Division of the Canadian Food Inspection Agency routinely scans external sources to identify information that might be of possible regulatory significance or interest to Canada's national plant health. This Plant Science Scan report was prepared by the Canadian Food Inspection Agency's staff as a mechanism to highlight potential items of interest, raise awareness and share significant new information related to plant health.

Index of Articles



Numbered squares correspond to numbered articles above

Canadian Food Inspection Agency | Agence canadienne d'inspection des aliments

Canada

000757

Pathology

1 New pest: New canker disease on poplar in Europe and Asia

In 2009, a new disease was observed on poplar (*Populus x euramericana*) trees in Hungary. The primary symptom of the disease was vertical cracks in the bark of the tree with a sticky, brown substance oozing from the canker. A bacterium was isolated from the ooze and named *Lonsdalea quercina* subsp. *populi* (Tóth et al., 2013). A paper in the journal *Plant Disease* reports that this bacterium has now also been identified on *Populus x euramericana* in China. Affected trees had symptoms of bark canker with frothy white exudates, and severely affected trees even died (Li et al., 2014).

A closely related species, *Lonsdalea quercina* subsp. *quercina*, has been identified as the causal agent of 'drippy nut disease' in oak in the USA (Brady et al., 2012). No records can be found in the scientific literature to suggest that either bacterium is present in Canada.

SOURCES: Brady C.L., Cleenwerck I., Denman S., Venter S.N., Rodríguez-Palenzuela P., Coutinho T.A. and De Vos P. (2012) Proposal to reclassify *Brenneria quercina* (Hildebrand & Schroth 1967) Hauben *et al.* 1999 into a novel genus, *Lonsdalea* gen. nov., as *Lonsdalea quercina* comb. nov., descriptions of *Lonsdalea quercina* subsp. *quercina* comb. nov., *Lonsdalea quercina* subsp. *iberica* subsp. nov., and *Lonsdalea quercina* subsp. *britannica* subsp. nov., emendation of the description of the genus *Brenneria*, reclassification of *Dickeya dieffenbachiae* as *Dickeya dadantii* subsp. *dieffenbachiae* comb. nov., and emendation of the description of *Dickeya dadantii*. International Journal of Systematic and Evolutionary Microbiology 62: 1592–1602.

Li, Y., He, W., Ren, F., Guo, L., Chang, J., Cleenwerck, I. Ma, Y. and Wang, H. (2014) A Canker Disease of *Populus x euramericana* in China caused by *Lonsdalea quercina* subsp. *populi*. Plant Disease 98(3): 368-378 DOI 10.1094/PDIS-01-13-0115-RE.

Tóth, T., Lakatos, T. and Koltay, A. (2013) *Lonsdalea quercina* subsp. *populi* subsp. nov., isolated from bark canker of poplar trees. International Journal of Systematic and Evolutionary Microbiology 63: 2309-2313 DOI 10.1099/ijs.0.042911-0.

2 Update: '*Candidatus* Phytoplasma prunorum' (European stone fruit yellow) in apricot orchards in the Czech Republic

A recent study provides an update on the status of '*Candidatus* Phytoplasma prunorum' (European stone fruit yellow) in the Czech Republic where the disease was reported more than 15 years ago. Long-term monitoring of '*Candidatus* Phytoplasma prunorum' in orchards concludes that the disease is an increasing concern for growers. A 50% infection level and an average of 30% of tree die-off (up to 40% in young trees) are reported in apricot orchards even when certified trees are being planted. Although disease symptoms are quite variable, chlorotic leaf-roll was the most common symptom observed in apricots during this study.

'*Candidatus* Phytoplasma prunorum' is known to be present in most European countries and causes important losses in apricot, peach and Japanese plum. It is considered a quarantine pest to Canada.

SOURCE: Nečas, T., Ondrásek, I. and Krska, B. (2015) 'Candidatus Phytoplasma prunorum' (European stone fruit yellow) - a pathogen spreading uncontrollably in apricot orchards in the Czech Republic. Acta Hortic 1105: 131-136 DOI: 10.17660/ActaHortic.2015.1105.19.

Entomology

3 Update: Ash tree resistance to the emerald ash borer

The emerald ash borer (EAB), *Agrilus planipennis* (Coleoptera: Buprestidae), is a regulated quarantine pest for Canada, present so far only in parts of Ontario and eastern Quebec. Prohibitions on the movement of ash material and firewood have been implemented to slow the spread of the pest and 'buy time' so that studies researching host resistance of ash to EAB might evolve to a point where treatments are available that could further hinder the pests' movement or save high-value trees.

Villari et al. (2016) recently reviewed the current literature to analyze mechanisms underlying inter- and intraspecific variation in ash resistance to EAB. The review made the following conclusions:

- Manchurian ash is less preferred for adult feeding and oviposition than susceptible North American species and more resistant to larval feeding (Chakraborty et al., 2014; Rigsby et al., 2014).
- Drought stress decreased the resistance of Manchurian ash, but had no effect on constitutive bark phenolics, suggesting that they do not contribute to increased susceptibility in response to drought stress (Chakraborty et al., 2014).
- Application of methyl jasmonate was associated with increased bark concentrations of verbascoside, lignin and/or trypsin inhibitors which decreased larval survival and/or growth in bioassays, suggesting that green, white and black ash possess potential for resistance that is not expressed under natural conditions (Whitehill et al., 2014).

The authors also point to an intriguing find that a very small proportion of green ash have survived in heavily EAB-attacked stands and suggest that these 'lingering ash' could provide material to study resistance traits. A recent study by Koch et al. (2015) investigated intraspecific variation in the 'lingering ash' referred to in an effort to identify specific traits or phenotypes that are likely to be associated with increased ability to survive EAB infestation. Three selections were significantly less preferred for adult feeding, but no specific leaf volatile was associated with reduced preference, and two selections had significant differences in larval development. The results indicate that more than one mechanism is likely responsible for providing resistance in certain ash trees. Koch et al. (2015) suggest continued monitoring and preservation of ash trees that fit the criteria of the 'lingering ash' which could lead to the identification of additional EAB-resistant selections of North American ash species and sources of resistance genes for breeding programs.

SOURCES: Chakraborty, S., Whitehill, J.G.A., Hill, A.L., Opiyo, S.O., Cipollini, D., Herms, D.A. and Bonello, P. (2014) Effects of water availability on emerald ash borer larval performance and phloem phenolics of Manchurian and black ash. Plant, Cell and Environment 37: 1009-1021.

Koch, J.L., Carey, D.W., Mason, M.E., Poland, T.M., and Knight, K.S. (2015) Intraspecific variation in *Fraxinus pennsylvanica* responses to emerald ash borer (*Agrilus planipennis*). New Forests 46: 995-1011.

Villari, C., Herms, D. A., Whitehill, J. G., Cipollini, D. and Bonello, P. (2016) Progress and gaps in understanding mechanisms of ash tree resistance to emerald ash borer, a model for wood-boring insects that kill angiosperms. New Phytologist 209: 63-79.

Whitehill, J.G.A., Rigsby, C.M. Cipollini, D., Herms, D.A., Bonello, P. (2014) Decreased emergence of emerald ash borer from ash treated with methyl jasmonate is associated with induction of general defense traits and the toxic phenolic compound verbascoside. Oecologia 176: 1047-1059.

4 New Pest: *Agrilus ribesi* goes undetected in North America for a century

The Eurasian species *Agrilus ribesi* was recently reported for the first time from North America (Jendek et al., 2015) and proposed to have caused damage to currants (*Ribes* spp.) in Ontario, previously ascribed to *A. cuprescens* (Garlick, 1940). The discovery was triggered by Garlick's record of black currant, red currant and gooseberry as host plants of *A. cuprescens* in Ontario which were refuted as such in the more recent list of verified host plants (Jendek, 2003; Jendek and Poláková, 2014). The biology of *A. cuprescens,* a notorious pest of *Rubus* and *Rosa,* is well documented, while its development in *Ribes* had never been confirmed, signalling the need for record re-evaluation. All specimens of *A. cuprescens* in the Canadian National Collection were critically examined and 16 of them were re-identified as those of *A. ribesi*.

Morphological diagnostic characters for the two *Agrilus* species are provided in the recent report (Jendek et al., 2015) and complemented with DNA barcodes for four alien *Agrilus* species established in North America (i.e., *A. ribesi, A. cuprescens, A. planipennis* and *A. sulcicollis*) to enable DNA-based identification. Low genetic variability of the North American populations of *A. cuprescens* and *A. ribesi* could indicate a single introduction to North America for each of these species.

SOURCES: Garlick, W.G. (1940) Notes on the rose stem girdler, *Agrilus communis rubicola* Abeille. Canadian Entomologist 72: 21-23.

Jendek, E. (2003) Revision of *Agrilus cuprescens* (Ménétriés, 1832) and related species (Coleoptera: Buprestidae). Zootaxa 317: 1-22.

Jendek, E., Grebennikov, V. and Bocak, L. (2015) Undetected for a century: Palaearctic *Agrilus* Schaefer (Coleoptera: Buprestidae) on currant in North America, with adult morphology, larval biology and DNA barcode. Zootaxa 4034(1): 112-126.

Jendek, E. and Poláková, J. (2014) Host plants of world *Agrilus* (Coleoptera: Buprestidae). A critical review. Springer, Berlin, 706 pp.

5 *Bactra bactrana*, a sedge-feeding leafroller, attacking greenhouse sweet peppers

A recent bulletin reports *Bactra bactana* (Lepidotpera: Tortricidae) attacking sweet peppers, *Capsicum annuum*, for the first time (Roditakis et al., 2015). The infestation was detected in two greenhouses in Southern Crete, Greece, where moth larvae caused typical symptoms of a fruit borer, including small holes on the surface of the peppers and internal damage due to feeding activity. Based on the observed infestation levels of 30% and 15% of fruit in the two greenhouses, *B. bactana* could be considered a potential pest of sweet pepper. Unknown factors are expected to have facilitated the major host shift as the moth coexists with peppers in other parts of Europe without causing damage.

Species from this genus have been used for the control of weeds. This find highlights the need for extensive host plant testing when considering the release of biocontrol agents. Although some associations cannot be predicted, host plants of clear economic value should be considered for inclusion in these tests, even if the range of known hosts of a control agent is narrow.

SOURCE: Roditakis, E., Morin, S. and Baixeras, J. (2015) Is *Bactra bactrana* (Kennel, 1901) a novel pest of sweet peppers? Bulletin of Entomological Research 1-7 DOI:10.1017/S0007485315000917.

Botany

6 First Report: *Orobanche* species parasitizing commercial sunflowers in the U.S.

In September 2014, *Orobanche ludoviciana* (Louisiana broomrape) was found parasitizing the roots of sunflower plants in a commercial sunflower production field in Kimball County, Nebraska. It was the first report of any *Orobanche* species parasitizing commercial sunflowers in the western hemisphere.

Orobanche species are obligate parasitic plants that establish vascular connections to roots of host plants from which they draw nutrients and water. *Orobanche cumana* is a well-known widespread and economically damaging pest of sunflowers in Europe. The species in question, *O. ludoviciana,* is native to North America and is widely dispersed in the Great Plains region. In Canada, it is found in southern British Columbia and the Prairie Provinces and is known to parasitize other members of the Asteraceae family (esp. *Ambrosia* and *Artemisia*) (Scoggan, 1979). The plants have pink stems and purple flowers, and arise from the base of the host plant.

In the affected field in Nebraska, about 30% of sunflowers in 25% of the total area of the field were parasitized by *O. ludoviciana.* The parasitized plants were significantly stunted, with smaller heads and thinner stalks. It is uncertain if yields were impacted. This new finding has raised some concern for sunflower growers in the Great Plains region.

In Canada, sunflowers represent a small but important part of the Prairie agricultural industry. Approximately 35,000 ha of sunflowers are seeded each year, resulting in an annual production of about 67,000 tonnes of sunflower seeds (Statistics Canada, 2015). *Orobanche* species are regulated at the genus level under Canada's *Plant Protection* Act; however, *O. ludoviciana* is an exception because it is a native plant in Canada. Awareness of this plant and its potential to parasitize sunflowers may be important for early detection and management of infections should they occur.

SOURCES: Harveson, R. M., Nelson, A., Mathew, F. M. and Seiler, G. J. (2015) First report of *Orobanche ludoviciana* parasitizing sunflowers. Plant Health Progress doi:10.1094/PHP-BR-15-0043.

Scoggan, H. J. (1979) Flora of Canada. National Museums of Canada, Ottawa.

Statistics Canada. (2015) Tables by subject: Crops and horticulture. Field and special crops. [Online] Available: http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/ind01/l3_920_2024-eng.htm?hili_prim11 [5 Jan 2016].

7 Pathway: Proposed changes to ballast water management – implications for invasive plants and plant pests

Ballast water has long been recognized as a significant vector for the transport and introduction of new invasive species both in Canada and around the world. Ballast is taken on board ships to control their stability and trim, but because it is typically taken up and released in different locations it can facilitate the rapid movement of species, sometimes over large distances. Ballast water is attributed with introducing a number of harmful invasive species in Canada, including zebra mussels, quagga mussels, round goby and spiny water flea in the Great Lakes Region, and others such as the green crab and common periwinkle in coastal areas. Ballast water and associated sediment can also be a vector for aquatic and wetland plants, and associated pests

and diseases.

In Canada, ballast water management (BWM) guidelines have been in place since the 1980s, and statutory regulations under the *Canada Shipping Act* have been in effect since 2006. Current regulations apply to all Canadian vessels worldwide, as well as non-Canadian vessels operating in waters under Canadian jurisdiction. They require ballast water to be treated, exchanged, transferred to a reception facility or retained on board, to minimize the possibility of spreading harmful organisms. By far the most common management method used in Canada and around the world is mid-ocean exchange (MOE), which works on the principle of differences in water conditions (primarily salinity) between source and exchange locations. For example, many ships take up and release ballast in freshwater ports, crossing the ocean in between. Exchanging the ballast mid-ocean exposes freshwater organisms to intolerable salinity levels, and ensures that ballast exchange occurs between ecologically different zones, thus lowering the risk of invasion. However, there are a number of limitations to existing regulations and the practice of MOE, particularly for vessels moving and practicing MOE within or between marine systems where salinity levels are similar.

In 2010, Canada ratified the International Maritime Organization (IMO)'s *International Convention for the Control and Management of Ships' Ballast Water and Sediments* (BWMC). This was the first attempt at an international, legally binding legislation for BWM, and will come into effect twelve months after ratification by 30 member states representing at least 35% of the world shipping tonnage (currently at 43 states and 32.54%). The convention introduces new requirements for on-board testing and concentration-based discharge standards (the "D-2 standards"), although the effectiveness of a number of treatment systems certified under this program have been called into question. Currently, Transport Canada is deliberating how to proceed with implementation of the IMO D-2 standards, and the exact nature and timing of any new BWM requirements at the national level remains unclear. In the meantime, Transport Canada has initiated discussions with the CFIA about possible implications of these new requirements for the risk associated with plants and plant pests that could be transported in ballast water or associated sediment.

SOURCES: Cohen, A. N. and Dobbs, F. C. (2015) Failure of the public health testing program for ballast water treatment systems. Marine Pollution Bulletin 91(1): 29-34.

Mills, E. L., Leach, J. H., Carlton, J. T. and Secor, C. L. (1993) Exotic species in the Great Lakes: A history of biotic crises and anthropogenic introductions. Journal of Great Lakes Research 19(1): 1-54.

Scriven, D. R., DiBacco, C., Locke, A. and Therriault, T. W. (2015) Ballast water management in Canada: A historical perspective and implications for the future. Marine Policy 59: 121-133.

Biotechnology

8 Review: The global outlook for genetically modified crops

The development and cultivation of genetically modified (GM) crops is increasing on a global scale. The global pipeline of GM crops is evolving, and this has implications for the international trade of agricultural commodities. In 2008, the European Commission's Joint Research Centre (JRC) examined the global situation of GM crops in development (Stein and Rodríguez-Cerezo, 2009). A follow-up document published in January 2016

(Parisi et al., 2016) reported that GM events nearly doubled from 2008 to 2015.

Diversity of GM crop types and traits are increasing at all stages of development. Crop types are currently dominated by maize, cotton, soybean and oilseed rape. However, biomass for liquid fuels and industrial products is becoming an important sub-sector of GM crops, driven by market demand. Rice and potatoes are also major upcoming GM crops, and cereals, fruits and vegetables are also under development in Brazil, India and China. Public developers in India and China are becoming increasingly active in GM crop development. New, smaller companies are emerging in the United States, India and other parts of Asia. Although herbicide-tolerance and insect-tolerance are the most dominant traits for GM crops, herbicide-tolerance traits are shifting from glyphosate and glufosinate to other active ingredients such as sulfonylurea, 2,4-D, dicamba, isoxaflutole and oxynil. New and emerging traits are being developed worldwide, particularly in Asia, including insect-resistant eggplant (India), insect-resistant poplar (China) and virus-resistant bean (Indonesia). Important traits in African countries include insect and disease tolerance, abiotic stress tolerance (i.e., drought) and biofortification for human nutrition in crops such as banana, cowpea and rice. The development of crops with more than one improved agronomic trait is becoming increasingly common. Known as 'stacked varieties', these may be developed using molecular tools or through conventional breeding of two or more plant lines with GM events. Stacked varieties are projected to play a major role in the development of upcoming GM crops. Unfortunately, there are large discrepancies in the regulatory treatment of stacked varieties across countries, which can result in asynchronous authorization.

In summary, the current trend towards increasing development and cultivation of GM crops in diverse geographic regions is projected to continue. Thus, there is a strong need for international dialogue to minimize the negative effects of asynchronous authorization on global agricultural trade.

SOURCES: Parisi, C., Tillie, P. and Rodríguez-Cerezo, E. (2016) The global pipeline of GM crops out to 2020. Nature Biotechnology 34(1): 31-36.

Stein, A.J. and Rodríguez-Cerezo, E. (2009) The global pipeline of new GM crops. Implications of asynchronous approval for international trade. European Commission, Joint Research Centre.

9 New Technology: The patent battle over CRISPR-Cas9 techniques

We often remark about the great potential of emerging technologies, but rarely do we observe them moving quickly from discovery to commercialization. CRISPR gene editing systems are certainly bucking this trend. Since 2012, when CRISPRs were first engineered to target specific genetic sequences *in vitro*, the technology has been used to successfully edit bacterial, fungal, animal and plant genomic sequences *in vivo*. Moreover, an intense foundational technology patent battle has emerged between scientists at the University of California, Berkley and the Broad Institute of MIT and Harvard. The outcome of this patent battle will influence hundreds of millions of dollars already committed to CRISPR-based companies.

The patent dispute traces back to March 15, 2013 when Jennifer Doudna and Emmanuelle Charpentier, of UC Berkley and the Max Plank Institute, respectively, filed for a joint CRISPR-Cas9 technique patent with the United States Patent and Trademark Office (USPTO). In October 2013, Feng Zhang of the Broad Institute of MIT filed to

protect his CRISPR-Cas9 technique using an expedited review. The Zhang patent was granted in April 2014, while the Doudna-Charpentier application was still being processed 2 years later. In January, 2016 the USPTO decided to review who should have been awarded the CRISPR-Cas9 patent; Doudna-Charpentier or Zhang. This process, called patent interference, functions much like a court case and will likely see both Doudna and Zhang deposed under oath with evidence used to establish what group invented the technique first. Many expect that laboratory notes will play a large part in establishing the timeline.

The outcome of these proceedings will be important for the agricultural biotechnology sector. Doudna's biotechnology start-up, Caribou Biosciences, recently announced a CRISPR-Cas9 patent sharing agreement with DuPont-Pioneer. Both groups possess CRISPR-Cas9 patents, and this partnership allows access to each other's CRISPR intellectual property. This partnership also divvies up the agricultural crop space; DuPont will develop crops like maize, soybean and canola, while Caribou Biosciences will be responsible for fruits and vegetables. If Doudna and Charpentier are unsuccessful in their interference challenge, then it's reasonable to expect that this Caribou Bioscience – DuPont partnership will have to restructure significantly, if it continues to exist at all.

For Canadian regulators, the outcome of this patent dispute may be interesting, but is unlikely to affect daily activities. Moreover, despite there being significant uncertainty over how CRISPR technologies will be treated by worldwide regulatory agencies, Canada's product based regulatory system is well positioned to address incoming Plants with Novel Traits derived from CRISPR-Cas9 tool sets.

SOURCES: Ledford, H. (2016) Bitter fight over CRISPR patent heats up. Nature 529, 265 doi:10.1038/nature.2015.17961.

Grushkin, D. (2016) DuPont in CRISPR-Cas patent land grab, Nature Biotechnology 34:1, 13 doi:10.1038/nbt0116-13.

Acknowledgments

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From: Christine Tibelius
Sent: 2016-04-05 9:52:54 AM
To: Sarah.Davis@inspection.gc.ca;France.Morin@inspection.gc.ca
CC: Cecile.Girard@inspection.gc.ca;Philip.Macdonald@inspection.gc.ca;Dylan.Levac@inspection.gc.ca
BCC:
Subject: Re: Please book appointment - Synthetic Biology

We should try and connect with Phil as well if we can still fit in a meeting this week. Otherwise, you and I can meet Sarah, then I can also consult with Phil.

Christine

>>> Sarah G. Davis 2016/04/05 8:57 AM >>>
Hi France,

It looks like Christine has a conflict at 11:00, so we'll have to find another time. Could you please include Cécile on the appointment? She's looking into the biotech team's notes on this file, and will dig up our response to a previous survey on synthetic biology we completed under the Cartagena Protocol which may prove useful.

Are we coordinating with Phil as well?

Sarah

>>> France Morin 2016-04-05 8:41 AM >>>
Hi Christine,

Dylan is away on conference travel returning April 9th and Sarah will be away on business travel (OECD Working Group meeting) for the next couple of weeks returning April 22, 2016.

I can schedule a meeting with you and Sarah this morning from 11:00 - 12:00, I will go ahead and send the appointment.

France

>>> Christine Tibelius 2016-04-04 5:24 PM >>>
Hi France,

Could you please book a 1 hour appointment in my office for Sarah, Dylan and I to discuss Synthetic Biology, asap when we are all free.

Thanks,


TEXT.htm

Christine

s.19(1)

From:
To:
CC:
Date: 2016/04/13 10:22 AM
Subject: Re: SynBio under the CBD

I just looked at the survey on SynBio, and tried to fill it out. I got as far as Question 10 and find that I have a problem with it. First of all, in the instructions, there is an error in how the scoring is defined. Then as one gets into the question further, the way the choices are set up is confusing relative to the introductory instructions. I wonder if anyone else is having problems interpreting how to answer the questions. For example, in the first response to the definition, should I click the button that best fits my opinion (operational definition or legislative definition), or as the instructions say, whether I strongly agree or disagree with the definition? Unless this is clear, and if others are having the same problem I am having, the results of this survey will be misleading and not useful.

Am I just being dense?

On Wed, Apr 13, 2016 at 3:31 AM,
> wrote:

> Dear All,
>
> Hope this finds you well.
>
> Following up on our communications about the Synthetic Biology discussions
> under the CBD, hereby a quick update and request for feedback:
>
> *SBSTTA *
>
> As discussed, SynBio is on the agenda of the 20th meeting of the
> Subsidiary Body on Scientific, Technical and Technological Advice (SBSTTA
> 20) which will meet from 25 - 30 April 2016 in Montreal, Canada.
>
> Information Note for Participants is available on the respective meeting
> webpages at:
>
> SBSTTA 20 - http://www.cbd.int/doc/?meeting=SBSTTA-20
>
> SBI 1 - http://www.cbd.int/doc/?meeting=SBI-01
>
>
>
> We know that Luciana Ambrozevicius and another Brazilian colleague will be
> attending and we hope that Lucia can participate on behalf of PRRI.
>
> Who else will attend?

>
>
>
> *SIDE EVENT ON SYNBIO*
>
> Several of us are discussing the possibility of a side event on SynBio
> during COP, with as particular aspect the possibility of bringing in young
> scientists (e.g. iGem). Maria is the driving force behind this. We will
> keep you posted on this.
>
>
>
> *SURVEY *
>
> Just in case you did not receive this: there is a survey among CBD
> stakeholders regarding the COP of the CBD that also touches on Synthetic
> Biology. The survey is being conducted as part of an international research
> project funded by the German Research Foundation and the results will no
> doubt be quoted at the COP.
> https://www.soscisurvey.de/cbd1/?d=8CBWFA8ZBPPUD9Y9
>
> For those of you who do not attend COPs, feel free to just choose "not
> applicable" and only answer the questions related to SynBio. Should not
> take you more than 5 mins.
>
>
>
> *GENE DRIVES *
>
> Earlier Boet Glandorf forwarded to this group some information on gene
> drives.
>
> Although several of you have indicated that they do not categorise gene
> drives as a form of Synthetic Biology, I take this opportunity to give you
> a quick update.
>
> Boet's update nicely coincided with plans that PRRI had to address this
> topic in a proactive manner. As a start we have produced a brief 'fact
> sheet' on the PRRI website (
> http://www.prri.net/scientific-topics/gene-drives/). Hector Quemada has
> kindly greed to lead a working group within PRRI to further explore the
> topic. Please have a look at the page and send us any comments you may
> have.
>
> We already received several requests of people on this list to be placed
> on an email list about gene drives. Please let us know in case you also
> wish to be placed on that list.
>
>
>
> *PAPERS/ARTICLES *
>
> Some recent articles that have received some attention :
>
>
> http://www.nature.com/news/minimal-cell-raises-stakes-in-race-to-harness-synthetic-life-

s.19(1)

1.19633?WT.mc_id=FBK_NatureNews
>
> http://www.geneticsandsociety.org/section.php?id=289
>
>
>
> Regards
>
>
>
>
>
>
>
>

s.19(1)

From:
To:
CC:
Date: 2016/05/02 12:34 PM
Subject: Re: Synthetic Biology - visions of the future SYNENERGENE Forum 24-25th June 2016 Amsterdam

Just for clarity, those applications don't involve a gene drive mechanism. They are male sterile strategies using a GE approach but don't drive through a population. They disappear.

On Monday, May 2, 2016, wrote:

> Hi,
>
> Gene Drives need is so obvious now with successful use in Brazil for Zika
> virus with 90% decrease in targeted mosquitoes and now release in US. It is
> important to say that the gene drives target a very specific species rather
> than many insects like pesticides, the alternative that is used, not to
> mention the effects on environment and humans. BTW, California has been
> effectively using gene drives for controlling leaf hoppers for virus in
> plants and pink boll worm in cotton, such that we need very little control
> using BT. Ironically, we use less GM as a result. This has been done by
> releasing sterile insects by irradiation of males.
>
> Arguing against this is selfish and egotistical.
>
> A no-brainer.
>
> best,
>
>
>
> -----Original Message-----
> From:
> Sent: Sunday, May 1, 2016 1:46 PM
> To:
> Cc:
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> Louter,Jim [NCR];
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>
> Philip
> Macdonald;
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>
> Subject: Re: Synthetic Biology visions of the future SYNENERGENE Forum
> 24-25th June 2016 Amsterdam
>
> Thanks to all for this thread.
>

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> It's important to be communicate that many believe that gene drives are
> not part of synbio. It is equally important to explain to the media, CBD,
> and NGOs where exactly gene drives do "belong"?
>
> Best wishes,
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> From:
> <javascript:;>>>
> Date: Sunday, May 1, 2016 at 1:08 AM
> To:
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> "Louter,Jim [NCR]" <jim.louter@ec.gc.ca <javascript:;><mailto:
> jim.louter@ec.gc.ca <javascript:;>>>,
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> Philip Macdonald <
> philip.macdonald@inspection.gc.ca <javascript:;><mailto:
> philip.macdonald@inspection.gc.ca <javascript:;>>>,
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> Subject: Re: Synthetic Biology - visions of the future SYNENERGENE Forum
> 24-25th June 2016 Amsterdam
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> Hi
> Thanks for the alert - we have added it to the page on SynBio on the PRRI
> site.
> I take this opportunity to ask those who attended SBSTTA what the final
> outcome was on the discussion on SynBio. We heard that the discussions were
> quite heated at one point.
> I also take this opportunity to respond to a question I received what the

s.19(1)

> feedback was on whether or not people consider gene drives as a form of
> Synbio. We received 7 responses, all saying that they did not consider gene
> drives as a form of SynBio.
> Wishing you all a great remainder of the Sunday!
>
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>
> On 28 April 2016 at 13:55,
> >> wrote:
> FYI
>
> Kind regards,
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> _____
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>
> RIVM/VSP
> PO Box 1 3720 BA Bilthoven
> The Netherlands
>
> Phone number:
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> Proclaimer RIVM http://www.rivm.nl/Proclaimer<
> http://www.rivm.nl/Proclaimer>
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From: Cheryl Dollard
To: Levac, Dylan
CC: Davis, Sarah G.; Macdonald, Philip; Tibelius, Christine
Date: 2016/05/05 11:21 AM
Subject: Fwd: "CRISPR/Cas9 in Drug Discovery: Applications in target discovery, validation, and hit screening" - SIGN UP NOW for our newest Science Webinar!

Received from Seed group - know you're interested, so sharing...
c

>>> Mark Forhan 2016-05-04 9:33 AM >>>
FYI - thought it might be of interest. It's pharma focussed but you all know the tech is transferrable to our areas of oversight

>>>

From: "Science Webinars" <sciencewebinars@aaas.sciencepubs.org>
To:<mark.forhan@inspection.gc.ca>
Date: 09:03 AM 2016-05-04
Subject: "CRISPR/Cas9 in Drug Discovery: Applications in target discovery, validation, and hit screening" - SIGN UP NOW for our newest Science Webinar!

(http://webinar.sciencemag.org/)

New complimentary webinar from *Science*:

CRISPR/Cas9 in drug discovery: Applications in target discovery, validation, and hit screening
You are invited to hear our panel of experts on May 11, 2016, in this live, online educational seminar. For more information and complimentary registration visit: **webinar.sciencemag.orgDate:** Wednesday, May 11, 2016
Time: 12 noon Eastern, 9 a.m. Pacific, 5 p.m. UK, 6 p.m. Central Europe
Duration: 1 hour
(http://view6.workcast.net/register?pak=8841844949903385&referrer=Blast2)
About This Webinar
The CRISPR/Cas9 system allows for unprecedented ease and control when editing the genome. Its potential impact on drug discovery is vast, including enabling gene and cell replacement therapies, identifying novel drug targets through functional genomic screens, and simplifying the production of disease models using permanent knockouts for validating therapy targets and testing drug efficacy. But in practical terms, how is CRISPR/Cas9 currently being applied, and where might the future challenges and pitfalls be? Furthermore, how do assays based on the new CRISPR/Cas9 technology compare with current screening methodologies, particularly those using small interfering RNA (siRNA)?
During the webinar, our expert panel will address:
• Areas of the drug discovery process where gene editing will have the most immediate and long term impact
• The current and future role of CRISPR/Cas9 in target discovery, hit identification, and lead optimization (compared with siRNA screening)
• The challenges that CRISPR/Cas9 brings to screening and assay development, particularly with respect to cell analysis
• The importance of carrying out binding studies following gene editing.
The presentations will be followed by a live Q&A session with the online audience.

Participants:

Lorenz Mayr, Ph.D.

AstraZeneca
Cambridge, U.K.
Ralph Garippa, Ph.D.
Memorial Sloan Kettering Cancer Center
New York, NY
Register at:
webinar.sciencemag.org
Questions? E-mail: webinar@aaas.org.
Produced by the *Science*/AAAS Custom Publishing Office and sponsored by:

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(http://view6.workcast.net/register?pak=8841844949903385&referrer=Blast2)
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This e-mail was sent to: mark.forhan@inspection.gc.ca
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+1 202-326-6417 | memuser@aaas.org | Privacy Policy (http://www.sciencemag.org/site/help/about/privacy.xhtml)

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From:
To:
CC:
Date: 2016/05/05 2:45 PM
Subject: Re: Synthetic Biology – visions of the future SYNENERGENE Forum 24-25th June 2016 Amsterdam

I would like to understand this more fully myself, and the recent responses have prompted me to weigh in to try to gain that understanding from the group on this email thread. As I have mentioned previously in past conference calls, I struggle to see that what we are doing under the activities we now call Synthetic Biology is qualitatively any different from what we were doing when we were genetically engineering things. We now have more sophisticated and powerful tools, but to use an analogy, whether we are using a hand saw and hammer or a power saw and nail gun, we would be still doing carpentry. And if we say we are using engineering principles, what do we mean exactly, and are we saying we were not doing so when were doing genetic *engineering?* What type of thinking were we not doing then that we are doing now? So with respect to gene drive, those constructs that drive through a population seem to me to be just newer implementations of the knowledge and capabilities that have been developed in the fields of molecular biology and genetics, which have underpinned genetic engineering from the beginning. Whether transgene insertions that drive through a population (a characteristic of the gene combinations inserted into a genome through genetic engineering techniques) are or are not a part of Synthetic Biology depends on what we agree Synthetic Biology is or even if it is an area of scientific endeavor that deserves a new name at all. Right now, I am reminded of the fable about the blind men and the elephant.

On Thu, May 5, 2016 at 1:37 PM,
wrote:

> I loathe to get into the defining Synthetic Biology argument and I very
> much fear that I might regret the contribution, but the lack of clear
> definition is clearly problematic in this conversation. The question of
> whether gene drives are synthetic biology does not have a simple answer - a
> synthetic gene drive is a tool that is a product of synthetic biology. It's
> like many tools that are the product of an engineering process: it can be
> used to engineer a new system or it can simply be used.
>
> The logic behind this answer is that synthetic biology is defined as the
> application of engineering principles (e.g. standardisation,
> modularisation, modelling, predictive design and abstraction hierarchies
> etc.) to biology and biotechnology. Synthetic biology is not limited to
> making changes to genomes since you can apply engineering principles to
> building with biological materials *in vitro* as well as in a cell. The
> insertion into, or modification of DNA in living cells is, however, where
> most of the community is working at present. Since we are not yet advanced
> to a stage where we can consider ourselves as true engineers, synthetic
> biology practitioners are mainly aiming to advance the science and
> technologies to enable the engineering of biology to be as predictable (and

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> as easy/cheap/reliable/repeatable etc.) as possible.
>
> While the successful invention of synthetic gene drive systems (and many
> other new biotechnolgies) may have required the application of engineering
> principles, it does not mean that the use of these tools in any other
> process is synthetic biology by default: Synthetic gene drives can be used
> in, for example, classical biology experiments 'to observe what might
> happen. In most cases being discussed in this group, the aim is to use them
> to use them to engineer a biological system as predictably as possible with
> predictive modelling done in advance to make a specific, desired outcome as
> certain possible. It's very hard to argue that this does not fall into the
> above definition of synthetic biology.
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> Engineering Biology The Genome Analysis
> Centre Norwich Science Park Norfolk, NR4 7UH, UK
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> <%2B44%20%280%291603%20450845>*
> ----------
> *From:* Friedman, Robert [rfriedman@jcvi.org]
> *Sent:* Thursday, May 05, 2016 5:24 PM
> *To:*
> *Cc:*
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> Louter Jim [NCR]:
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> Philip
> Macdonald;

> *Subject:* RE: Synthetic Biology – visions of the future SYNENERGENE
> Forum 24-25th June 2016 Amsterdam
>
> Hi all—
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>
> Just a quick response to the query whether gene drives are a form of
> synbio. I was surprised to read that all seven responders replied “no”. I
> guess that is technically correct, but perhaps misleading. Hints of the
> “process vs product” debate here…
>

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>
> In my view, synthetic biology is a process: a group of methods that can be
> used to genetically modify an organism. An organism with a gene drive is
> the product. The drive is a trait that can be engineered into an organism
> (and, in fact, is sometimes found in nature).
>
>
>
> Decades of prior gene drive research did not use what we now call
> synthetic biology techniques. (Nor were they particularly successful.)
> But in my view, the recent burst of activity to add a desired gene with the
> ability to drive through a population (using CRISPR or other modern
> systems) has relied on the synthetic biology techniques. A good review of
> the different types of gene drive systems is here:
> http://www.nature.com/nrg/journal/v17/n3/abs/nrg.2015.34.html Champer,
> Buchman, and Akbari, "Cheating evolution: gene drives to manipulate the
> fate of wild populations" Nature Reviews Genetics.
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> J. Craig Venter Institute
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> 4120 Capricorn Lane, La Jolla, CA 92037
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> phone:
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> cell phone:
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> *From:*
> *Sent:* Sunday, May 01, 2016 1:08 AM
> *To:* Boet Glandorf
> *Cc:*
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> On 28 April 2016 at 13:55, wrote:
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> FYI
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> Kind regards
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> RIVM/VSP
> PO Box 1 3720 BA Bilthoven
> The Netherlands
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> Phone number: +
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> Proclaimer RIVM http://www.rivm.nl/Proclaimer
> <http://www.rivm.nl/Proclaimer>
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From: Ewa Madey
Sent: 2016-05-25 9:41:40 AM
To: Philip.Macdonald@inspection.gc.ca;Cindy.Pearson@inspection.gc.ca;Dylan.Levac@inspection.gc.ca;Christine.Tibelius@inspection.gc.ca;andrew.atkinson@canada.ca;anthony.ridgway@canada.ca;azam.tayabali@canada.ca;brian.belliveau@canada.ca;brooke.walter@canada.ca;deborah.ashby@canada.ca;genevieve.bondy@canada.ca;george.arvanitakis@canada.ca;jason.rancourt@canada.ca;jim.louter@canada.ca;karen.reynolds@canada.ca;megan.bettle@canada.ca;neil.macintosh@canada.ca;phil.shwed@canada.ca;rick.scroggins@canada.ca;sabrina.kim@canada.ca;souad.elouakfaoui@canada.ca;souleh.semalulu@canada.ca;stephanie.hardy@canada.ca;titus.tao@canada.ca;jflamenbaum@cihr-irsc.gc.ca;david.lee@hc-sc.gc.ca;Jenna.Griffiths@hc-sc.gc.ca;kirsten.jacobsen@phac-aspc.gc.ca;
CC: kathrina.yambao@canada.ca;
BCC:
Subject: Re: SAVE THE DATE: Health Portfolio Synthetic Biology Workshop

Hello
are there space constraints? Can I send more than one person to the workshop?
thanks

Ewa Madey, Ph.D.
(613) 773-7754| Ewa.Madey@inspection.gc.ca | Facsimile / Télécopieur : (613) 773-7754
National Manager, Fertilizer Safety Office, Plant Health & Biosecurity Directorate/CFIA
Gestionnaire Nationale Bureau de l'innocuité des engrais, Direction de la protection et biosécurité des végétaux/ACIA

59 Camelot Drive | 59 Camelot Drive, Ottawa, ON K1A 0Y9
Government of Canada | Gouvernement du Canada www.inspection.gc.ca
>>> 2016-05-25 8:19 AM >>>
Hi Andy,

Sorry for the delay, we've been away. I have no problem in inviting the folks in question.

Possibly consider inviting from U of Ottawa??

Regards,

Brian

From: "Atkinson, Andrew (HC/SC)" <andrew.atkinson@canada.ca>
To: "Tayabali, Azam (HC/SC)" <azam.tayabali@canada.ca>; "Arvanitakis, George (HC/SC)" <george.arvanitakis@canada.ca>; "Ashby, Deborah (HC/SC)" <deborah.ashby@canada.ca>; "Bettle, Megan (HC/SC)" <megan.bettle@canada.ca>; "Shwed, Phil (HC/SC)" <phil.shwed@canada.ca>; "Rancourt, Jason (HC/SC)" <jason.rancourt@canada.ca>; "Semalulu, Souleh (HC/SC)" <souleh.semalulu@canada.ca>; "Reynolds, Karen (HC/SC)" <karen.reynolds@canada.ca>; "Bondy, Genevieve (HC/SC)" <genevieve.bondy@canada.ca>; "Hardy, Stephanie (HC/SC)" <stephanie.hardy@canada.ca>; "Ridgway, Anthony (HC/SC)" <anthony.ridgway@canada.ca>; "david.lee@hc-sc.gc.ca" <david.lee@hc-sc.gc.ca>; "Belliveau, Brian (HC/SC)" <brian.belliveau@canada.ca>; "Tao, Titus (HC/SC)" <titus.tao@canada.ca>; "Walter, Brooke (HC/SC)" <brooke.walter@canada.ca>; "Jacobsen, Kirsten (PHAC/ASPC)" <kirsten.jacobsen@phac-aspc.gc.ca>; "Macdonald, Philip (CFIA/ACIA)" <Philip.Macdonald@inspection.gc.ca>; "Tibelius, Christine (CFIA/ACIA)" <Christine.Tibelius@inspection.gc.ca>; "Levac , Dylan (CFIA/ACIA)" <Dylan.Levac@inspection.gc.ca>; "Pearson, Cindy (CFIA/ACIA)" <Cindy.Pearson@inspection.gc.ca>; "Madey, Ewa (CFIA/ACIA)" <Ewa.Madey@inspection.gc.ca>; "jflamenbaum@cihr-irsc.gc.ca" <jflamenbaum@cihr-irsc.gc.ca>; ; "Scroggins, Rick (EC)" <rick.scroggins@canada.ca>; "El Ouakfaoui, Souad (EC)" <souad.elouakfaoui@canada.ca>; "MacIntosh, Neil (IC)" <neil.macintosh@canada.ca>; "Kim, Sabrina (IC)" <sabrina.kim@canada.ca>; "Griffiths, Jenna (HC/SC)" <Jenna.Griffiths@hc-sc.gc.ca>; "Louter, Jim (EC)" <jim.louter@canada.ca>
Cc: "Yambao, Kathrina (PHAC/ASPC)" <kathrina.yambao@canada.ca>;
Sent: Friday, May 20, 2016 4:17 PM
Subject: FW: SAVE THE DATE: Health Portfolio Synthetic Biology Workshop

Dear all,

This is a SAVE-THE-DATE notice for an upcoming Health Portfolio Synthetic Biology Workshop facilitated by

Wednesday June 15, 2016, 09h00 - 16h00 (PHAC Media Room, 120 Colonnade Road).

An agenda and additional logistics will follow, as well as a calendar request.

Many of you have already been interviewed by who has been commissioned to identify potential regulatory or process gaps related to synthetic biology oversight throughout the Health Portfolio. The insights from the interviews will flow into a workshop backgrounder and a final report.

The workshop is an essential part of this process as it will allow us to collectively set priorities and - if there are any issues worthy of serious consideration - discuss ideas for solutions. We also wish to identify regulatory sectors not impacted by synthetic biology, regardless of novelty. This output will be used to better frame pressing issues for communication to senior management as well as assist with public communication.

Issues to be discussed may include risk analysis and regulations, human resources and expert capacity, communication and knowledge management, international issues and collaboration, etc.

In addition, we are considering opening the workshop with two external speakers:

- (Concordia University) will talk about Synthetic Biology, and its likely practical applications which will require regulatory oversight.
- We would also like to invite a representative from BioteCanada to briefly share thoughts on Synthetic Biology and regulatory issues they foresee.

and BioteCanada's role at this event will be specific; this is simply an opportunity for these speakers to briefly share their views, and answer questions we may for them. Once their talks are complete, the speakers will leave the meeting and the workshop will continue in-camera.

If you have any concerns about inviting these individuals or organizations, please contact me as soon as possible.

Regards

Andy

TEXT.htm

From: "Flamenbaum, Jaime (CIHR/IRSC)" <Jaime.Flamenbaum@cihr-irsc.gc.ca>
Sent: 2016-06-01 4:24:28 PM
To:
Ewa.Madey@inspection.gc.ca;Philip.Macdonald@inspection.gc.ca;Cindy.Pearson@inspection.gc.ca;Dylan.Levac@inspection.gc.ca;Christine.Tibelius@inspection.gc.ca;andrew.atkinson@canada.ca;anthony.ridgway@canada.ca;azam.tayabali@canada.ca;brad.feasey@canada.ca;brian.belliveau@canada.ca;brooke.walter@canada.ca;deborah.ashby@canada.ca;genevieve.bondy@canada.ca;george.arvanitakis@canada.ca;jason.rancourt@canada.ca;jim.louter@canada.ca;karen.reynolds@canada.ca;luc.bourbonniere@canada.ca;megan.bettle@canada.ca;neil.macintosh@canada.ca;neil.strand@canada.ca;phil.shwed@canada.ca;rick.scroggins@canada.ca;sabrina.kim@canada.ca;souad.elouakfaoui@canada.ca;souleh.semalulu@canada.ca;stephanie.hardy@canada.ca;titus.tao@canada.ca;david.lee@hc-sc.gc.ca;Jenna.Griffiths@hc-sc.gc.ca;kirsten.jacobsen@phac-aspc.gc.ca
CC: kathrina.yambao@canada.ca;
BCC:
Subject: RE: SAVE THE DATE: Health Portfolio Synthetic Biology Workshop *** Postponment Until the week of October 11-14 ***

Just a reminder: October 12 is Yom Kippur (Day of Attunement) the major Jewish religious holiday. You may have scheduling conflicts with invitees who profess that religion.

Jaime Flamenbaum, MD MSc

Senior Ethics Advisor / Science, Knowledge Translation and Ethics
Canadian Institutes of Health Research / Government of Canada
Jaime.flamenbaum@cihr-irsc.gc.ca / Tel: 613-941-4640

Conseiller principal en matière d'éthique / Sciences, Application des connaissances et Éthique
Instituts de recherche en santé du Canada / Gouvernement du Canada
Jaime.flamenbaum@cihr-irsc.gc.ca / Tél: 613-941-4640

[http://intranet/sites/default/files/gocsig-wordmark-eng.jpg]

From: Atkinson, Andrew (HC/SC) [mailto:andrew.atkinson@canada.ca]
Sent: Monday, May 30, 2016 11:41 AM
To: Tayabali, Azam (HC/SC); Arvanitakis, George (HC/SC); Ashby, Deborah (HC/SC); Bettle, Megan (HC/SC); Shwed, Phil (HC/SC); Rancourt, Jason (HC/SC); Semalulu, Souleh (HC/SC); Reynolds, Karen (HC/SC); Bondy, Genevieve (HC/SC); Hardy, Stephanie (HC/SC); Ridgway, Anthony (HC/SC); david.lee@hc-sc.gc.ca; Belliveau, Brian (HC/SC); Tao, Titus (HC/SC); Walter, Brooke (HC/SC); Jacobsen, Kirsten (PHAC/ASPC); Macdonald, Philip (CFIA/ACIA); Tibelius, Christine (CFIA/ACIA); Levac , Dylan (CFIA/ACIA); Pearson, Cindy (CFIA/ACIA); Madey, Ewa (CFIA/ACIA); Flamenbaum, Jaime (CIHR/IRSC); briancolton@rogers.com; Scroggins, Rick (EC); El Ouakfaoui, Souad (EC); MacIntosh, Neil (IC); Kim, Sabrina (IC); Griffiths, Jenna (HC/SC); Louter, Jim (EC); Strand, Neil (HC/SC); Bourbonniere, Luc (HC/SC); Feasey, Brad (IC)
Cc: Yambao, Kathrina (PHAC/ASPC);
Subject: RE: SAVE THE DATE: Health Portfolio Synthetic Biology Workshop *** Postponment Until the week of October 11-14 ***

Dear all,

We've received feedback from participants, and it appears that June 15th conflicts with a number of previously scheduled meetings.

Given that we are running into summer months, we are postponing this event until the week of October 11-14.

Please let us know whether you'll likely have a conflict with that timing.

Take care all,

Andy

Andrew Atkinson
Manager, Emerging Sciences Policy / Gestionnaire, Politiques des sciences émergentes
Science Policy Directorate/Direction des politiques scientifiques
Strategic Policy Branch/Direction générale de la politique stratégique
Health Canada | Santé Canada
Phone: 613-948-8095
Cell: 613-851-7284
Fax: 613-941-9093

Brooke Claxton Building | édifice Brooke Claxton, Room | pièce 967D
70, promenade Colombine Driveway, Pré Tunney's Pasture, Ottawa, Ontario K1A 0K9
Postal Locator | Indice postal : 0909C

From: Atkinson, Andrew (HC/SC)
Sent: 2016-05-20 4:17 PM
To: 'azam.tayabali@hc-sc.gc.ca'; 'george.arvanitakis@hc-sc.gc.ca'; 'deborah.ashby@hc-sc.gc.ca'; 'megan.bettle@hc-sc.gc.ca'; 'Phil.shwed@hc-sc.gc.ca'; 'Jason.Rancourt@hc-sc.gc.ca'; 'Souleh.semalulu@hc-sc.gc.ca'; 'karen.reynolds@hc-sc.gc.ca'; 'Genevieve.bondy@hc-sc.gc.ca'; 'Stephanie.hardy@hc-sc.gc.ca'; 'Anthony.ridgway@hc-sc.gc.ca'; 'david.lee@hc-sc.gc.ca'; 'Brian.belliveau@hc-sc.gc.ca'; 'titus.tao@hc-sc.gc.ca'; 'Brooke.walter@hc-sc.gc.ca'; 'Kirsten.jacobsen@phac-aspc.gc.ca'; 'philip.macdonald@inspection.gc.ca'; 'christine.tibelius@inspection.gc.ca'; 'dylan.levac@inspection.gc.ca'; 'Cindy.Pearson@inspection.gc.ca'; 'Ewa.Madey@inspection.gc.ca'; 'jflamenbaum@cihr-irsc.gc.ca'; 'briancolton@rogers.com'; 'rick.scroggins@canada.ca'; 'souad.elouakfaoui@canada.ca'; 'Neil.Macintosh@canada.ca'; 'Sabrina.Kim@canada.ca'; Griffiths, Jenna (HC/SC); Louter, Jim (EC/EC)
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Regards

Andy


TEXT.htm


image001.jpg


Mime.822

From: "Flamenbaum, Jaime (CIHR/IRSC)" <Jaime.Flamenbaum@cihr-irsc.gc.ca>
Sent: 2016-06-01 4:29:06 PM
To:
Ewa.Madey@inspection.gc.ca;Philip.Macdonald@inspection.gc.ca;Cindy.Pearson@inspection.gc.ca;Dylan.Levac@inspection.gc.ca;Christine.Tibelius@inspection.gc.ca;andrew.atkinson@canada.ca;anthony.ridgway@canada.ca;azam.tayabali@canada.ca;brian.belliveau@canada.ca;brooke.walter@canada.ca;deborah.ashby@canada.ca;genevieve.bondy@canada.ca;george.arvanitakis@canada.ca;jason.rancourt@canada.ca;jim.louter@canada.ca;karen.reynolds@canada.ca;megan.bettle@canada.ca;neil.macintosh@canada.ca;phil.shwed@canada.ca;rick.scroggins@canada.ca;sabrina.kim@canada.ca;souad.elouakfaoui@canada.ca;souleh.semalulu@canada.ca;stephanie.hardy@canada.ca;titus.tao@canada.ca;david.lee@hc-sc.gc.ca;Jenna.Griffiths@hc-sc.gc.ca;kirsten.jacobsen@phac-aspc.gc.ca;
CC: kathrina.yambao@canada.ca;
BCC:
Subject: RE: SAVE THE DATE: Health Portfolio Synthetic Biology Workshop

Andrew.

I have to appologise: I have a major conflict with June 15. Sorry for not being able to attend

Jaime Flamenbaum, MD MSc

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From: Atkinson, Andrew (HC/SC) [mailto:andrew.atkinson@canada.ca]
Sent: Friday, May 20, 2016 4:17 PM
To: Tayabali, Azam (HC/SC); Arvanitakis, George (HC/SC); Ashby, Deborah (HC/SC); Bettle, Megan (HC/SC); Shwed, Phil (HC/SC); Rancourt, Jason (HC/SC); Semalulu, Souleh (HC/SC); Reynolds, Karen (HC/SC); Bondy, Genevieve (HC/SC); Hardy, Stephanie (HC/SC); Ridgway, Anthony (HC/SC); david.lee@hc-sc.gc.ca; Belliveau, Brian (HC/SC); Tao, Titus (HC/SC); Walter, Brooke (HC/SC); Jacobsen, Kirsten (PHAC/ASPC); Macdonald, Philip (CFIA/ACIA); Tibelius, Christine (CFIA/ACIA); Levac , Dylan (CFIA/ACIA); Pearson, Cindy (CFIA/ACIA); Madey, Ewa (CFIA/ACIA); Flamenbaum, Jaime (CIHR/IRSC); briancolton@rogers.com; Scroggins, Rick (EC); El Ouakfaoui, Souad (EC); MacIntosh, Neil (IC); Kim, Sabrina (IC); Griffiths, Jenna (HC/SC); Louter, Jim (EC)
Cc: Yambao, Kathrina (PHAC/ASPC);
Subject: FW: SAVE THE DATE: Health Portfolio Synthetic Biology Workshop

Dear all,

This is a SAVE-THE-DATE notice for an upcoming Health Portfolio Synthetic Biology Workshop facilitated by

Wednesday June 15, 2016, 09h00 - 16h00 (PHAC Media Room, 120 Colonnade Road).

An agenda and additional logistics will follow, as well as a calendar request.

Many of you have already been interviewed by who has been commissioned to identify

potential regulatory or process gaps related to synthetic biology oversight throughout the Health Portfolio. The insights from the interviews will flow into a workshop backgrounder and a final report.

The workshop is an essential part of this process as it will allow us to collectively set priorities and - if there are any issues worthy of serious consideration - discuss ideas for solutions. We also wish to identify regulatory sectors not impacted by synthetic biology, regardless of novelty. This output will be used to better frame pressing issues for communication to senior management as well as assist with public communication.

Issues to be discussed may include risk analysis and regulations, human resources and expert capacity, communication and knowledge management, international issues and collaboration, etc.

In addition, we are considering opening the workshop with two external speakers:

- (Concordia University) will talk about Synthetic Biology, and its likely practical applications which will require regulatory oversight.
- We would also like to invite a representative from BioteCanada to briefly share thoughts on Synthetic Biology and regulatory issues they foresee.

and BioteCanada's role at this event will be specific; this is simply an opportunity for these speakers to briefly share their views, and answer questions we may for them. Once their talks are complete, the speakers will leave the meeting and the workshop will continue in-camera.

If you have any concerns about inviting these individuals or organizations, please contact me as soon as possible.

Regards

Andy


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From:
To: "'philip.macdonald@inspection.gc.ca'" <philip.macdonald@inspection.gc.ca>
Date: 2016/06/08 12:35 PM
Subject: Guest Speaker Invitation: CRISPR Precision Genome Editing Congress Europe 2016
Attachments: CRISPR & Precision Genome EditingCongress Europe 2016 - Preliminary Agenda.pdf

Dear Phil,

I hope this finds you well. I was recommended to get in touch regarding a speaking invitation to this year's CRISPR Precision Genome Editing Congress Europe taking place on 24th-26th October in Berlin - a forum for leading biopharma and academic figureheads as they reveal advanced methodology, strategies and clinical timelines to fulfil the revolutionary promise of precision genome editing.

Having established a series of CRISPR Precision Genome Editing events<http://crispr-congress.com/> within the US, we are working with the our partners and the community to put together a Europe-centric forum this year.

Given your position and vast expertise within the field, I'm delighted to extend to you an invitation to join as an official speaker for this year's European meeting, also benefiting from a complimentary pass to the entire event.

The ultimate purpose of the summit is to enhance and improve the very latest applications of CRISPR within basic research and biomedical research. Overcome key specificity, efficiency & delivery challenges to pioneer drug discovery, biomedical research and therapeutic applications of precise genome engineering.

Main areas of discussion will include:

Ø Scalpel Precision: Empowering CRISPR to be Even More Precise

Ø Improving Customised Design of CRISPR Workflows & Effective Data Analysis

Ø Advancing Disease Modelling & Large Scale Genome Wide Screening

Ø Regulatory Landscape of CRISPR Across Industries

Ø Clinical Utility: Therapeutic Applications of CRISPR

Ø Pioneering CRISPR in Drug Discovery and Target Identification

Confirmed speakers include:

Oncology Pharmacology, Novartis Institutes for BioMedical Research

WU Agrotechnology and Food Sciences, Wageningen UR

Terrestrial Microbiology, Max-Planck-Institute

Pfizer

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Netherlands

Cancer Institute

Takeda Cambridge

Cellectis

I have attached the draft agenda for you to review and welcome the opportunity to collaborate on confirming your speaking position in a relevant session.

My initial thoughts are that you would be a fantastic fit the panel discussion entitled 'Navigating the Regulatory Environment for CRISPR as Novel Breeding Technique' at 9.05am on Conference Day Two, 26th October.

As such, are you available for a 10-15min call tomorrow or Friday to discuss this speaking opportunity further?

Please do let me know your interest, as I finalize the official program.

Many thanks for your consideration and looking forward to your reply shortly.

Best wishes,

Hanson Wade

[cid:image001.jpg@01D1AC87.C2A80A10]
52 Grosvenor Gardens | London | SW1W 0AU
Direct Line: |

Pages 789 to / à 794

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From:
To: <philip.macdonald@inspection.gc.ca>
Date: 2016/06/27 6:49 PM
Subject: Confirmed to be Chair/Speaker at ICG 2017

2nd Annual International Congress of Genetics ICG-2017
April 25-27, 2017 | Xi'an, China
Homepage | Schedule | Program Layout| Register

Dear Philip Macdonald,

We are honored to announce that the 2nd Annual International Congress of Genetics (ICG-2017) will be held during April 25-28, 2017 in Xi'an, China. On behalf of the organizing committee, I am writing to you to propose a Speech as a speaker/chair at the Session 202: CRISPR and Precise Genome Engineering Techniquesand talk about the latest discovery in A comparative analysis of insertional effects in genetically engineered plants: considerations for p.... If this proposal session is not your interested one, please check the program online at http://www.bitcongress.com/icg2017 and inform me your decision. We believe that your participation will add great value for ICG-2017.

ICG successfully began with 2016, there were nearly 100 participants from over 20 countries and areas have attended the ICG-2016. Participants from academic, industrial professionals and key-decision makers delivered the new achievement on their research, together discussed and analysis the development of Genetics. ICG-2017 will be a grand meeting with hundreds of people in the field of genetics, it will bring us a big breakthrough. depending on the warmly support and valuable suggestions from all of the participants.

A rich selection of topics will be addressed during ICG-2017, which includes:
Branch 1: Breakthrough in Basic Science of Genetics and Genome
Branch 2: The Up-to-date Genetic Technologies and Application
Branch 3: Human Genetics
Branch 4: Animal Genetics
Branch 5: Plant and Microbial Genetics
Branch 6: Gene Industry's Today and Tomorrow

Xi'an enjoys the title of "A Natural Museum of History", it has been the most popular tourist city in China and the World owing to its brilliant historical and cultural relics, and spring is the most pleasant season for a visit.

We expect your precious comments or suggestions; also your reference to other speakers will be highly appreciated. We look forward to receiving your replies on the following questions:

1. What is the title of your speech?

2. Do you have any suggestions about our program?

We look forward to seeing you in Xi'an in 2017 for this influential event.

Sincerely yours,

Organizing Committee of ICG-2017

Contact:

Organizing Commission of ICG-2017

s.19(1)

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