s.19(1)

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

s.19(1)

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.
>

s.19(1)

> 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

s.19(1)

>>
<https://www.whitehouse.gov/sites/default/files/microsites/ostp/modernizing_the_reg_system_for_biotech_products_memo_final.pdf>
>> *
>>
>>
>>
>> best,
>>
>>
>>
>>
>>
>> *From:*
>> *Sent:* Monday, November 9, 2015 2:05 PM
>> *To:*
>> *Cc:*
>>
>>
>>
>>
>>
>>
>>
>>
>> Philip Macdonald;
>>
>>
>>
>>
>> *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'.
>>
>>

>>
>> 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.
>>
>>
>>
>>
>>
>> Ciao!
>>
>>

s.19(1)

>>
>>
>>
>>
>>
>> On 26 October 2015 at 19:31,
>> wrote:
>>
>>
>>
>>
>>
>> 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.
>>
>>
>>
>>
>>
>>
>>
>>
>>

s.19(1)

>>
>>
>>
>>
>> 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

s.19(1)

>> 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 !
>>
>>
>>
>>
>>
>>

>>
>>
>>
>> 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.

s.19(1)

>>
>> 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
>>
>>
>>
>>
>>

s.19(1)

>> PS: Below some recent articles on NBTs.
>>
>>
>>
>>
>>
>> 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
>>
>>
>>
>>
>>
>> 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>