**template for Peer Review comments**

**Technical series on synthetic biology**

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|  | **This form compiles comments from experts from several Government of Canada departments and should not be construed as reflecting official positions of the Government of Canada.** |
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| **Comments on the Technical Series on Synthetic Biology** |
| **Page #** | **Line #** | **Comment** |
| 0 | 0 | Off target effectsThe analysis of potential risk of off-target effects does not fully place the potential risk of off-target effects into the larger context of genetic changes that may occur through spontaneous or conventional breeding, nor does it indicate how off-target effects can be observed and mitigated. Please see Schnell et al, 2014:[A comparative analysis of insertional effects in genetically engineered plants: considerations for pre-market assessments | SpringerLink](https://link.springer.com/article/10.1007/s11248-014-9843-7). Although this paper does not deal with synthetic biology applications, it does present a discussion around the spontaneously occurring genetic changes that happen in plants (transposons, NHEJ, conventional breeding, etc) and a summary of risk assessment of positional effects as unintended genetic changes. For example, the following excerpts regarding mitigation of risk from Schnell et al, 2014 may provide more context :“As has already been discussed, the relationship between genotype and phenotype is complex and it is also tempered by the environment. Genetic changes may be introduced into plants spontaneously or through conventional breeding or genetic engineering. The buffering capabilities of plant genomes and the quality control systems in plant cells will prevent many of these genetic changes from giving rise to discernible changes in a plant’s phenotype.”“Cultivar development typically requires upwards of 10 years and involves the evaluation of thousands of plants, resulting in the selection of one or very few final cultivars. Throughout breeding and seed production, selection is applied to eliminate off-types, which are those plants that show an unintended trait.”“The processing and preparation of foods and feeds may also play a role in managing the risks associated with genetic changes. For example, processing conditions that involve heat or pressure may significantly reduce the levels of toxins and/or anti-nutrients in the food or feed before consumption, so that any genetic changes that alter the levels of such compounds do not present a safety concern.” |
| 9 | 40 | The word “off” should be added following the word “pressure” to fully realize the meaning of the sentence. |
| 10 | 45 | Missing period following “bacteria”.  |
| 11 | 20 | The word “topical” is likely meant to say “tropical”. |
| 12 | 23 | Appears to be an incomplete sentence. |
| 12 | 40-45 | Health Canada has engaged in a number of regulatory foresight exercises in the past on synthetic biology, and biotechnology more broadly, involving information gathering on the latest research and development activities in these areas that are aiming at commercial application. This has allowed us to better determine how effectively our current regulatory systems can address any risks and whether changes in policy, regulation or regulatory capacity may be required. Suggest adding text here encouraging regulatory agencies to conduct such regulatory foresight exercises on a regular basis. |
| 19 | 31 | It looks like the word “of” should be inserted between the words “populations” and “insects”. |
| 20 | 10 | It looks like the word “in” should be inserted between the words “present” and “almost”. |
| 27 | 15  | What does this first sentence mean? Vibrant but basic seems contradictory. |
| 31 | 5-10 | Cloning is not typically considered “synthetic biology”, so suggest re-considering the relevance of the example of the black-footed ferret presented here. |
| 31 | 25-26 | “Using Cibus’ Rapid Trait Development SystemTM (ODM), *Brassica napus* acetohydroxyacid synthase 26 was mutated to confer tolerance to imidazolinone herbicides (Cibus, 2014; Schopke et al., 2008).”The description of a Cibus herbicide-tolerant canola product is inaccurate. Cibus’ herbicide-tolerant canola Line 5715 contains a mutation that confers tolerance to a herbicide (sulfonylurea). While a gene editing technique known as oligonucleotide-directed mutagenesis (ODM) was used within the developer’s Rapid Trait Development System™ (RTDS™), the mutation used in Event 5715 arose independently through spontaneous somaclonal variation. More information about the approved product can be found in this [published CFIA Decision Document (2013-100](https://inspection.canada.ca/plant-varieties/plants-with-novel-traits/approved-under-review/decision-documents/dd-2013-100/eng/1427383332253/1427383674669)), particularly under Section III. Description of the Novel Trait; 1. Development Method, and this [published Health Canada document](https://www.canada.ca/en/health-canada/services/food-nutrition/genetically-modified-foods-other-novel-foods/approved-products/novel-food-information-cibus-canola-event-5715-imidazolinone-sulfonylurea-herbicide-tolerant.html) under 2. Development of the Modified Plant. |
| 40 | 1 | Formatting, “Lin et al. ( 2020)reviewed” has 2 instances of incorrect spacing. |
| 40 | 3 | Formatting, incorrect spacing “levels(Wan…”  |
| 45 | 16-19 | “ Conversely, the cause of some of this imprecision is also being exploited by developers to intentionally modify more than one related sequence (with less than 100 percent sequence identity) in attempts to modify different alleles or homologous genes in the host organism at the same time (Lema, 2021)”The Lema 2021 paper is cited in the report, but there is no discussion on the methods proposed within to detect and regulate off-target DNA changes following genome editing: Bioinformatics identification of potential off target sites can be combined with whole genome sequencing (or directed sequencing) to confidently identify both small genetic changes and larger insertions or rearrangements. |
| 48 | 39-43 | “Society as a whole therefore has a key role to play in helping decision-makers and regulators better define specific protection goals (or “assessment endpoints”) i.e. the things that society doesn’t want harmed (Section 6.), that then dictates the characteristics of new products or technologies from synthetic biology to be assessed both scientifically (Craig et al., 2017) and socio-economically (Secretariat of the Convention on Biological Diversity, 2018).” Although society as a whole can help decision makers and regulators better define protection goals, please note the scope of Article 26\* of the Cartagena Protocol, where Parties may take into account Socio-economic considerations (SECs): * arising from the impact of LMOs,
* limited to the conservation and sustainable use of biological diversity
* consistent with international obligations

SECs could influence risk management, but the assessment of SECs should not be part of the risk assessment process, which should be based in science. The use of non-science based approaches to evaluating SEC of LMOs, if applied exclusively in risk assessments, could lead to an inconsistency with WTO obligations. \*Article 26The parties, in reaching a decision on import under this Protocol or under its domestic measures implementing the Protocol, may take into account, consistent with their international obligations, socio-economic considerations arising from the impact of LMOs on the conservation and sustainable use of biological diversity, especially with regard to the value of biological diversity to indigenous and local communities. |
| 51 | 40 | Double closed parentheses at the end of the line. |
| 52 | 16-17 | How did they come to the conclusion? Brief reasoning would help clarify, as previous lines indicate that the effect of synthetic alternatives are not clear with regards to the impacts on poaching. |
| 57 | 44-45 | Suggest the sentence be re-written as follows: “Some considerations regarding risk assessment for three synthetic biology supported technologies that have received considerable regulatory attention to date are presented below.” |
| 59 | 10 | The word “breeding” was likely meant instead of “breading”. |
| 62 | 8-20 | The engineering of auxotrophic mutations is another approach to induce conditional lethality in bacterial cells by requiring the addition of a particular nutrient into the media to maintain viability. A good example of this approach is found here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4579030/ |
| 62 | 21 | Suggest the title include the words “…for gene drives”, as this section appears to focus exclusively on gene drives. |
| 66 | 42-45 | This does not appear to be supported by any statements expressed in the Ellens et al. 2019 paper. In the abstract of the paper it states: “…*from a regulatory standpoint the Government of Canada views gene editing as another tool that will join current methods used to develop desirable traits in plants and animals. This is because Canada focusses on the potential risk resulting from the novelty of the trait, or plant or animal product entering the Canadian environment or market place, rather than the process or method by which it was created.*” Thus, it may be more accurate to say that plants, animals and their derived products (food, feed) produced through gene editing are regulated in Canada and subject to assessment based on whether novel traits are being expressed as a result of gene editing. |
| 67 | 11-12 | It would be helpful to state who has put forward these arguments and cite a few sources. |
| 67 | 15-18 | Suggest removing the last 2 sentences of this paragraph as they sound ambiguous and unfocused and do not appear to fit with the tone of the rest of the section. |
| 69 | 7-8 | Synthetic biology in unnecessary quotations. |
| 70 | 7 | Self-regulation in unnecessary quotations, as the term was defined and explained in the paragraph above.  |
| 70 | 17 | Formatting. Space required between “…2011)involving” |
| 70 | 27 | Formatting consistency. Elsewhere in the document, there is spacing between et al. and the bracketed year. In this line it is written as “et al.(2009)”. |
| 81 | 41-42 | Both SBSTTA and AHTEG are acronyms that have been previously spelled out, and therefore do not need to be spelled out again.  |
| 83 | 23-28 | Unclear as to why the phrase living modified organism is being put in quotation marks. The first instance may be quoting the Cartagena protocol, but the following instances are simply using the term.  |
| 84 | 3-24 | Comment as above, why is the term living modified organism being placed in quotation marks. Additionally, consider either spelling out the phrase OR using the acronym LMO (after the first time) for consistency.  |
| 96 | 27-29 | Why is this sentence bolded? If quoting the WHO, place in quotation marks.  |
| 101 | 6 | Phrasing/Formatting. Consider either: “At its 17th meeting in 2016” or “At its 17th meeting (CoP17, 2016)”. |
| 101 | 35 | Formatting. Elsewhere in the document, instances of “th”, “st”, and “nd” following a number are superscript. In this line, it is written as “70th”. |
| 105 | 13 | Formatting. If you abbreviate a name/term later, place the abbreviation in parentheses following the first time the phrase is used. In this case “The international Court of Justice (ICJ)” would be appropriate. |
| 111 | 20-21 | Awkward phrasing. Consider “The Indigenous and Tribal Peoples Convention, 1989 (No. 169), also known as ILO-Convention 169, is an International Labour Organization Convention which as of March 2021 has been ratified by 23 countries.” |
| 133 | 30 | “Fully” does not need to be placed in parentheses.  |
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Please submit your comments to secretariat@cbd.int.