Global Industry Coalition

Submission of Information on Synthetic Biology

Ref: SCBD/SPs/DC/DA/MW/86375 of 16-March-2017

16-June-2017

The Global Industry Coalition (GIC)[1] is pleased to make the following submission of information on synthetic biology in response to the request of the Executive Secretary[2] for "information and supporting documentation" on six topics elaborated in Decision XIII/17 of the Conference of the Parties to the Convention on Biological Diversity ("CBD") of 16 December 2016.[3] In this submission, the GIC provides a summary of its views on synthetic biology in an introductory section, then addresses topics A-F outlined in the decision and notification.

Introduction and Background for this Submission

The GIC is of the view that synthetic biology is part of the continuum of biotechnological development spanning more than four decades since recombinant DNA applications became feasible in the 1970s. Synthetic biology is not a new scientific field or paradigm, rather "synthetic biology" is an umbrella term encompassing accumulated and constantly advancing knowledge and understanding in biological engineering[4]. The scientific literature shows that the term is used to represent a heterogeneous mix of activities spanning established (and re-labelled) biotechnological methods, to biotechnological innovations[5]. For example, "synthetic biology" ranges from genetically modified microorganisms developed using established recombinant DNA tools for the production of chemicals[6], to early research concepts such as xenobiology[7]. As a consequence, no international consensus has been reached, or is likely to be achieved, on an operational definition of "synthetic

[1] The Global Industry Coalition (GIC) for the Cartagena Protocol on Biosafety receives input and direction from trade associations representing thousands of companies from all over the world. Participants include associations representing and companies engaged in a variety of industrial sectors such as plant science, seeds, agricultural biotechnology, food production, animal agriculture, human and animal health care, and the environment.

[2] Notification Ref: SCBD/SPS/DC/DA/MW/86375 of 16 March 2017.

[3] CBD/COP/DEC/XIII/17.

[4] Raimbault B, Cointet J-P, Joly P-B (2016) Mapping the emergence of synthetic biology, *PLoS ONE* DOI:10.1371/journal.pone.0161522.

[5] E.g. see Raimbault B, Cointet J-P, Joly P-B (2016) Mapping the emergence of synthetic biology.

[6] E.g. Ro D-K, Paradise EM, Ouellet M, Fisher KJ, Newman KL, Ndungu JM, Ho KA, Eachus RA, Ham TS, Kirby J, Chang MCY, Withers ST, Shiba Y, Sarpong R, Keasling JD (2006) Production of the antimalarial drug precursor artemisinic acid in engineered yeast, *Nature* 440: 940-943.

[7] E.g. see Schmidt M (2010) Xenobiology: a new form of life as the ultimate biosafety tool, *BioEssays* 32: 322-331.

biology", and the GIC believes that it is not possible to define it in a way that is meaningful and future-proof for the purpose of the discussions under CBD.

Biotechnological approaches, and any resulting living organisms, that may be labelled (or re-labelled) by some as "synthetic biology" are subject, where appropriate, to the range of existing national, regional and international regulatory mechanisms that apply to biotechnology. Where the product of a "synthetic biology" approach is non-living, e.g. chemicals and pharmaceuticals, it will be regulated, as appropriate, by existing applicable sectorial regulatory regimes governing their safe use and trade. These views are shared by many Parties that are engaged in synthetic biology discussions under the CBD. This submission primarily focusses on genetically modified/engineered organisms, or "living modified organisms" ("LMOs"), used in/resulting from "synthetic biology" approaches, as these are the predominant subject of current discussions under the CBD.

The Cartagena Protocol on Biosafety to the CBD ("Cartagena Protocol"), including its risk assessment and risk management provisions, provides an international regulatory framework for releases of LMOs into the environment. The GIC believes that the examples of "synthetic biology" cited in the current CBD discussions and the scientific literature are within the scope of "biotechnology" as defined by the CBD, and "modern biotechnology" as defined by the Cartagena Protocol. Furthermore, living organisms resulting from certain "synthetic biology" applications are LMOs as defined by the Cartagena Protocol. The GIC wishes to point out that in previous synthetic biology work under the CBD, and on risk assessment under the Cartagena Protocol, experienced biotech regulators could not identify specific examples of current and foreseeable synthetic biology applications that presented novel regulatory challenges or biosafety risks that could not be managed using established regulatory approaches[8]. These approaches are consistent with the Cartagena Protocol and have been used for more than 20 years in the assessment of biotech crops for release into the environment.

The GIC welcomes the invitation to submit information based on evidence which draws on real-world experience, and emphasizes that an extensive body of knowledge and expertise exists for products of biotechnology, both for contained use and for release into the environment. The GIC encourages Parties and other governments to share their actual results and experience, e.g. through

[8] E.g., see the online forum discussion on "Possible considerations during environmental risk assessment of LMOs developed or created through approaches commonly referred to as 'synthetic biology'" at http://bch.cbd.int/onlineconferences/2014_2016period.shtml.

the Biosafety Clearing House (BCH), to contribute to ensuring that synthetic biology discussions and decision-making under the CBD are informed by evidence and scientifically sound. The GIC hopes that this information submission will assist the deliberations of the Open-ended Online Forum and the Ad Hoc Technical Expert Group on Synthetic Biology, and that an appropriate course of action is taken in any future work on synthetic biology under the CBD. The GIC wishes to emphasize that such work should be focused on realistic applications and timeframes, and informed by relevant real-world experience, credible and peer-reviewed scientific evidence, and actual examples of biotechnological developments in areas that are likely to have adverse effects on the conservation and sustainable use of biodiversity. Such an approach would help to build better consensus and understanding of the issues amongst parties, reduce the complexity and ambiguity of the discussion, and focus action towards appropriate risk governance of the field.

A. Research, cooperation and activities noted in paragraph 9 of decision XIII/17

In response to the activities laid out in paragraph 9 (subparagraphs 9(a), 9(b) and 9(c)) of decision XIII/17, the GIC believes that it is unnecessary to start work on the development of guidance on assessing potential benefits and potential adverse effects of organisms, components and products of synthetic biology. We do not see the differentiating characteristics of the current and foreseeable applications of "synthetic biology" with those of "biotechnology" (as defined by the CBD) and "modern biotechnology" (as defined by the Cartagena Protocol). As detailed in Section B below, many of the benefits aspired to for "synthetic biology" and the potential adverse effects claimed by some are not new or unique – they are the same as that postulated for biotechnology since the 1970s. Furthermore, benefits have been realized with the use of biotechnology (see Section B below), and potential adverse effects managed according to established risk assessment and risk management processes (detailed in Sections C and D below).

We also emphasize that working on updating and adapting current methodologies for risk assessment of LMOs is not warranted unless and until credible evidence is available from actual applications demonstrating that existing regulatory frameworks and risk assessment methodologies are inadequate for products of "synthetic biology". In previous synthetic biology work under the CBD as well as the Online Forum on Risk Assessment and Risk Management under the Cartagena Protocol[9], regulators experienced in assessing LMOs concluded that existing risk assessment approaches remain adequate for applications that may be considered "synthetic biology" (see

[9] Ibid.

Section C below). Furthermore, these same experts were unable to identify existing or realistically foreseeable LMO that could not be managed using existing approaches. This expert position demonstrates an absence of gaps in existing risk assessment processes. It was also evident in these Online Forum discussions that there are knowledge gaps due to a lack of, or incomplete understanding of, the existing regulatory framework and risk assessment approaches for LMOs. Such knowledge gaps do not require the establishment of new or updated risk assessment guidance, but rather a better understanding of existing provisions.

As we note above and discuss further below, there is a substantial body of knowledge, experience and expertise with environmental releases of LMOs that is relevant to the consideration of the potential environmental impacts of LMOs resulting from "synthetic biology" applications. The GIC strongly supports efforts to promote the exchange of information and sharing of experiences in synthetic biology discussions under the CBD, particularly by regulators and other stakeholders that are involved in the development and assessment of biotechnological products. This will contribute to a better understanding amongst Parties and other governments of realistic potential benefits and adverse effects that "synthetic biology" may bring based on relevant factual evidence and real-world experience. The most effective approach to identifying any potential gaps would be to monitor biotechnological developments in areas that are likely to have adverse effects on the conservation and sustainable use of biodiversity. Less credence should be given to broad claims that are not substantiated by evidence, or isolated examples without context, about potential adverse effects as such assertions are rarely based on factual information.

B. Evidence of benefits and adverse effects of synthetic biology vis-à-vis the three objectives of the CBD

As we have noted in the Introduction, we consider "synthetic biology" to be part of the continuum of biotechnological development, that examples that have been cited in discussions under the CBD and in the scientific literature fall within the scope of "biotechnology" as defined by the CBD and "modern biotechnology" as defined by the Cartagena Protocol, and that living organisms used in/resulting from certain "synthetic biology" applications are LMOs. For this submission, we have focused on reviewing the published literature to provide evidence of the actual environmental impacts of existing products of biotechnology, with plants, particularly agricultural crops, being the products for which we have the most evidence. We also consider developments in other biotech sectors, and anticipated impacts of foreseeable biotech products that are in development. Impacts

are considered in the context of the CBD objectives of conservation and sustainable use of biological diversity, meaning that only applications with an actual or potential direct or indirect environmental impact are taken into account.

Biotech crops, developed by the introduction of specific novel traits, have been grown commercially throughout the world for more than 20 years[10]. These crops have been developed using the now-established recombinant DNA techniques, and the concerns raised today about the potential adverse effects of "synthetic biology" are the same as those that were raised earlier for biotechnology as a whole, and for biotech crops in particular. A survey of plant "synthetic biology" applications in the literature indicates that today, "synthetic biology" is a conceptual approach[11,12] for engineering plants, and these approaches remain within the broader field of biotechnology. Further, we could not identify any examples of plants developed using "synthetic biology" (either self-defined or identified in the CBD on-line forum) that differ from existing biotech plants. Examples highlighting our point include bioluminescent plants developed using routine and well established technology that dates back to the 1980s[13,14], also "metabolic engineering" to develop oilseed "bioenergy" crops[15], and the stacking of multiple genes in crops[16].

In the CBD discussions in particular, there are also examples of plant products of "synthetic biology" that do not differ to existing conventional (non-biotech) plants. A case in point is the often cited example of "new" biotechnologies such as genome editing[17,18]. However, genome editing is better described as an enabling tool[19], and like recombinant DNA technologies, genome editing may be used in various applications. Plants developed with certain genome editing methods are comparable to biotech plants, while others are comparable to plants developed with conventional breeding tools. Either way, the environmental impacts of such plants will be comparable to those of crops

[10] James C (2016) Global status of commercialized biotech/GM crops: 2016, ISAAA Brief No. 52-2016.
[11] E.g. Liu W, Stewart CN (2015) Plant synthetic biology, *Trends in Plant Science* 15:309-317.
[12] E.g. Medford JL, Prasad A (2014) Plant synthetic biology takes root, *Science* 346:162-163.
[13] E.g. Ow DW, De Wet JR, Helinski DR, Howell SH, Wood KV, Deluca M (1986) Transient and stable expression of the firefly luciferase gene in plant cells and transgenic plants, *Science* 234:856-859.
[14] Science for Environment Policy (2016) Synthetic biology and biodiversity, Future Brief 15; available at http://ec.europa.eu/science-environment-policy.
[15] Shih PM, Liang Y, Loque D (2016) Biotechnology and synthetic biology approaches for metabolic engineering and bioenergy crops, *Plant Journal* 87:103-117.
[16] Ibid.
[17] Zhang K, Raboanatahiry N, Zhu R, Li M (2017) Progress in Genome Editing Technology and Itslications in plants, *Frontiers Plant Science*, 8:177 doi: 10.3389/fpls.2017.00177.
[18] Songstad DD, Petolino JF, Voytas DF, Reichert NA (2017) Genome editing in plants, *Critical Reviews in Plant Science* doi: 10.1080/07352689.2017.1281663.
[19] Baltes NJ, Voytas DF (2015) Enabling plant synthetic biology through genome engineering, *Trends in Biotechnology* 33:120-31.

developed with earlier breeding tools – conventional or biotech. Thus, in our review of the literature, we have not identified a "new" plant biotech application that presents a fundamental change from existing biotech or non-biotech plants, and for both there is extensive evidence for environmental impacts.

CropLife International has compiled an extensive, publicly-available, up-to-date database containing published literature that demonstrates the benefits of biotechnology in agriculture[20]. A representative list of publications from this database summarizing general benefits associated with biotech crops with broad literature support is appended to this document (Appendix I).

The CropLife International database provides evidence for biotech crops that is directly relevant to the objectives of the CBD, spanning agronomic, environmental, and safety and health benefits, as well as developing country and socio-economic benefits (see Section F below for more detail). Within the database there are currently 258 publications identifying benefits arising from changes in agricultural practices with the adoption of biotech crops, including improvements in soil fertility, reduced chemical inputs, and yield improvements. With regard to agriculture in the developing world, there are 129 publications demonstrating benefits including safer and more effective means of controlling insect and virus pests that especially challenge farmers in tropic agricultural systems, and providing small farmers with more secure yields and reducing the pressure to clear land for agricultural production. It is also shown that between 1996-2015, the cumulative farm income gain derived by developing country farmers was USD 86.1 billion[21].

The literature in the CropLife International database on environmental benefits of biotech crops is extensive, with 331 publications showing improved agricultural productivity accompanied by reduced environmental impact. For example, the adoption of herbicide tolerant biotech crops has reportedly resulted in reduced soil erosion and improved soil quality due to the adoption of "no-till" and "reduced-till" farming systems, while insect resistant (Bt) crops have reduced impacts on non-target organisms. These are impacts that contribute to improving biological diversity in agricultural ecosystems. Changes in agricultural practices have also contributed to decreased greenhouse gas emissions through reduced fuel use and increased carbon sequestration. Reduced fuel use attributable to reduced chemical application alone resulted in permanent savings in carbon dioxide emissions amounting to about 2.8 billion kg (reduced fuel use of 1.1 billion liters) in 2015; over the

[20] http://biotechbenefits.croplife.org/.
[21] Brookes G, Barfoot P (2017) GM crops: global socio-economic and environmental impacts 1996-2015, PG Economics, United Kingdom.

period 1996-2015 the cumulative permanent reduction in fuel use is estimated at 26.2 billion kg of carbon dioxide (reduced fuel use of 9.8 billion liters). The additional carbon sequestration in 2015 alone resulting from changed tillage practices is estimated to be equivalent to removing 10.62 million cars from the roads[22].

Biotechnology has also been applied in other sectors, with its potential to deliver more efficient applications in the human health sector recognized since the early 1980s. Advancements facilitated by improved availability of genomic sequences and understanding of gene function have enabled the use of engineered microbes for the production of natural compounds such as human insulin and growth hormone, as well as vaccines, antibiotics, and antibodies with diagnostic and therapeutic applications[23]. The majority of these applications involve production and use under contained conditions, and they are not intended for environmental release. Further, their use in containment will be subject to established standards for microbial handling, import, transport, storage and disposal in order to prevent adverse impacts on human health and the environment[24,25].

Beyond the human health sector, biotechnological advancement since the 1980s have also contributed to the establishment of "industrial biotech", which comprises a diverse range of applications including biodegradation of waste, and the cost-effective production of fuel, polymers and other chemicals[26], many of which have today been re-labelled as "synthetic biology". In the scientific literature, most "synthetic biology" applications involve the use of engineered microorganisms (e.g. algae, yeast, bacteria) as host cells for the production of compounds, and these are promoted as having great potential to replace fossil-fuel based production systems for energy,

[22] Ibid.
[23] An up to date summary of biopharmaceutical products is available at: BIOPHARMA®: Biopharmaceutical Products in the U.S. and European Markets http://www.biopharma.com/.
[24] E.g. see: Office of the Gene Technology Regulator, Risk assessment and risk management plan for DIR 137 – Commercial supply of genetically modified live attenuated influenza vaccines, January 2016. Available at: http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/dir137/$FILE/Risk%20Assessment%20and%20Risk%20Management%20Plan.pdf.
[25] E.g. see: Office of the Gene Technology Regulator, Risk assessment and risk management plan for DIR 132 – Commercial supply of a tumour-selective genetically modified virus for cancer therapy, August 2015. Available at: http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/dir132/$FILE/Full%20Risk%20Assessment%20and%20Risk%20Management%20Plan.pdf.
[26] Jones MD, Fayerman JT (1987) Industrial applications of recombinant DNA technology. Weber State College Chem I Supplement. Volume 64 Number 4, 337- 339. Available at: http://pubs.acs.org/doi/pdf/10.1021/ed064p337.

materials and chemicals[27,28,29]. Such biological production systems are considered to have lower environmental impact than the industrial processes they replace. For example, they may have lower energy input requirements, reduced carbon dioxide emissions, and may not require extraction of non-renewable resources[30]. As such, there is significant investment in these "synthetic biology" applications, particularly for biofuels[31], and they are considered important for economic development[32]. While most of these applications involve production under contained conditions, e.g. in industrial fermenters, and are not intended for unconfined environmental release, their use in containment will be subject to regulatory procedures for microorganisms under containment established since the early 1980s[33,34]. Other industrial applications may utilize outdoor production systems, and while these are still confined, concerns have been raised in synthetic biology discussions under the CBD about the potential for escapes of engineered microbes. For example, a recent report described an evaluation of engineered alga performance in open pond production in the first trial of its type to be approved by the United States Environment Protection Agency (EPA)[35]. This report showed stability of the intended engineered traits, no increase in dispersal ability in the engineered alga, and no adverse impacts on the diversity or composition of native algae populations.

Another area of industrial biotech that is promoted in the scientific literature as having great potential is bioremediation[36,37,38], and this would involve releases of LMOs into the environment. Bioremediation utilizes the ability of microorganisms to detoxify, degrade or convert pollutants in

[27] Fesenko E, Edwards R (2014) Plant synthetic biology: a new platform for industrial biotechnology, *Journal of Experimental Botany* 65:1927-1937.
[28] Erb TJ, Zarzycki J (2016) Biochemical and synthetic biology approaches to improve photosynthetic CO_2-fixation, *Current Opinion in Chemical Biology* 34:72-79. https://doi.org/10.1016/j.cbpa.2016.06.026.
[29] Clarke LJ, Kitney RI (2016) Synthetic biology in the UK – an outline of plans and progress, *Synthetic and Systems Biotechnology* 1:243-257.
[30] OECD (2011) Future Prospects for Industrial Biotechnology, Organization for Economic Cooperation and Development, Paris.
[31] Shih PM, Liang Y, Loque D (2016) Biotechnology and synthetic biology approaches for metabolic engineering and bioenergy crops, *Plant Journal* 87:103-117.
[32] OECD (2011) Future Prospects for Industrial Biotechnology, Organization for Economic Cooperation and Development.
[33] World Health Organization, Laboratory Biosafety Manual (3rd ed, 2004).
[34] US Dept Health and Human Services, Centers for Disease Control and Prevention, National Institutes of Health – Biosafety in Microbiological and Biomedical Laboratories (5th ed, 2009).
[35] Szyjka SJ, Mandal S, Schoepp N, Tyler BM, Yohn CB, Poon YS, Villareal S, Burkart MD, Shurin JB, Mayfiedl SP (2017) Evaluation of phenotype stability and ecological risk of a genetically engineered alga in open pond production, *Algal Research* (in press) available at: http://dx.doi.org/10.1016/j.algal.2017.04.006.
[36] Singh S, Kang Sh, Mulchandani A, Chen W (2008) Bioremediation: environmental clean-up through pathway engineering, *Current Opinion in Biotechnology* 19:437-44.
[37] Cases I, de Lorenzo V (2005) Genetically modified organisms for the environment: stories of success and failure and what we have learned from them, *International Microbiology* 8:213-222.
[38] Ozcan F, Kahramanogullari CT, Kocak N, Yildiz M, Haspolat I, Tuna E (2012) Use of genetically modified organisms in the remediation of soil and water resources, *Fresenius Environmental Bulletin* 21:3443-3447.

contaminated environments. As such, release of LMOs into the environment for bioremediation is relevant to the objectives of the CBD. Many naturally occurring microorganisms have bioremedial properties, but their use is limited by slow metabolic rates and difficulties with scaling up from controlled conditions in reactors to field applications. The potential for biotechnology to develop microorganisms with improved efficacy has been investigated since the 1970s with a field-scale release of (chemically killed) recombinant microbes reported in 2000[39]. To date, biotechnology has been used in bioremediation with limited success due to poor microbe competitiveness and ability to survive in the target environment[40]. Advances with engineered microbes have also been limited by the existing regulatory constraints on their release into the environment[41,42].

The promise of "synthetic biology" to overcome the difficulties of bioremediation applications has been discussed in the literature for more than a decade, especially in regard to the ability to specifically design microbes with improved viability[43,44]. For the same reason, "synthetic biology" is considered to be a promising tool for designing improved microbes as biosensors to detect contamination[45]. Engineered microbes have also had limited success as biosensors due to poor sensitivities, selectivity and response rates, however biosensors are typically used in in vitro assays not released into the environment[46]. A recently reported example of a release into the environment is the small-scale research field test of a bacterial sensor strain sprayed onto soil to detect landmines[47]. The authors note several challenges to this application, including the viability of strains in different soils and climatic conditions, mechanisms for reducing the risk of transfer of genetic

[39] Strong LC, McTavish H, Sadowsky MJ, Wackett LP (2000) Field-scale remediation of atrazine-contaminated soil using recombinant *Escherichia coli* expressing atrazine chlorohydrolase, *Environmental Biology* 2:91-98.
[40] Singh S, Kang Sh, Mulchandani A, Chen W (2008) Bioremediation: environmental clean-up through pathway engineering, *Current Opinion in Biotechnology* 19:437-44.
[41] Cases I, de Lorenzo V (2005) Genetically modified organisms for the environment: stories of success and failure and what we have learned from them, *International Microbiology* 8:213-222.
[42] Ozcan F, Kahramanogullari CT, Kocak N, Yildiz M, Haspolat I, Tuna E (2012) Use of genetically modified organisms in the remediation of soil and water resources, *Fresenius Environmental Bulletin* 21:3443-3447.
[43] Singh S, Kang Sh, Mulchandani A, Chen W (2008) Bioremediation: environmental clean-up through pathway engineering, *Current Opinion in iotechnology* 19:437-44.
[44] Cases I, de Lorenzo V (2005) Genetically modified organisms for the environment: stories of success and failure and what we have learned from them, *International Microbiology* 8:213-222.
[45] Stenuit BL, Eyers L, Schuler SN, Agathos, George I (2008) Emerging high throughput approaches to analyze bioremediation of sites contaminated with hazardous and/or recalcitrant wastes, *Biotechnology Advances* 26:561-575.
[46] Viebahn M, Smit E, Glandorf DCM, WernarsK , Bakker PAHM (2009) Effect of genetically modified bacteria on ecosystems and their potential benefits for bioremediation and biocontrol of plant diseases – a review, in *Sustainable Agriculture Reviews 2: Climate Change, Intercropping, Pest Control, and Beneficial Microorganisms* (Eric Lichtfouse ed, SpringerLink).
[47] Belkin S , Yagur-Kroll S, Kabessa Y, Korouma V, Septon T, Anati Y, Zohar-Perez C, Rabinovitz Z, Nussinovitch A, Agranat AJ (2017) Remote detection of buried landmines using a bacterial sensor, *Nature Biotechnology* 25:308-309.

material to local soil bacteria, and removing the bacteria after they have served their purpose, and highlight the need for further research. It therefore remains questionable whether environmental releases of engineered microbes for bioremediation and biosensor applications are realistically foreseeable, given the reported technical challenges. In terms of regulation, microbes engineered using "synthetic biology" approaches will be LMOs subject to the same stringent regulatory oversight as microbes engineered using established biotechnological tools.

To conclude, we welcome the invitation to provide evidence of the impacts of current and foreseeable applications of biotechnology relevant to the request for information on synthetic biology in the context of the objectives of the CBD. We wish to emphasize the importance of deliberations and decision-making based on evidence rather than speculation of potential impacts, whether beneficial or adverse. We also stress the importance of the quality of information used to inform the debate. Furthermore, there is a growing voice coming from the conservation community[48] counselling prudent caution regarding restrictions on biotechnology that have potential beneficial applications for conservation. Based on the evidence presented above, and decades of experience with releasing biotech crops into the environment, it is evident that biotechnology has provided benefits to agriculture, despite claims by some to the contrary. Debates on the impacts of applications and products considered to be "synthetic biology" should take this real-world experience into account.

C. Experiences in conducting risk assessments of organisms, components and products of synthetic biology, including any challenges encountered, lessons learned and implications for risk assessment frameworks

We have established above that we consider "synthetic biology" to be part of the continuum of biotechnological development, and that examples cited in the discussions under the CBD and scientific literature are within the scope of "biotechnology" as defined by the CBD, and "modern biotechnology" as defined by the Cartagena Protocol. Furthermore, we consider the organisms resulting from certain "synthetic biology" applications to be "LMOs" as defined by the Cartagena Protocol, therefore the risk assessment principles and methodologies of Annex III apply.

[48] Redford KH (2014) Synthetic biology offers extraordinary opportunities and challenges for conservation, *Park Science* 31:30-34.

In Section B above, we note that biotech crops are the products of biotechnology intended for environmental release for which we have the most experience, and that these have been assessed according to the principles laid down in Annex III of the Cartagena Protocol. A search of risk assessments conducted for "LMOs for introduction into the environment" as a part of a regulatory review in the BCH[49] returns 911 records posted by 30 Parties and other governments spanning at least three decades. Other compilations of information on biotech crops note that 753 approvals for commercial cultivation of biotech crops that have been granted up to 2016[50]. Information about approvals and the risk assessments used in granting these can be found on publicly available databases maintained by the International Life Sciences Institute[51], and the International Service for the Acquisition of Agri-Biotech Applications[52]. The latter includes more than 400 transgenic events of biotech crops, trees, fruit species, and ornamental species, and spans more than 20 years[53]. Also available in the BCH are compilations of environmental risk assessment literature for biotech plants, which were submitted by the GIC in 2009[54] and 2012[55]. An updated list of recent risk assessment publications (since 2012) is appended to this document (Appendix II).

The risk assessment principles and methodologies in Annex III are derived from the foundational work of the National Academy of Sciences (NAS) of the United States[56] and the OECD[57] on regulation of products of biotechnology. These include: scientific soundness recognizing expert advice, a basis in scientific evidence, a comparative and a case-by-case approach directed by the characteristics of the LMO, its intended use and the likely receiving environment. The Cartagena Protocol also requires proportional risk management measures to prevent adverse effects identified via the risk assessment. The risk assessment principles and methodologies in Annex III allow for necessary flexibility depending on the characteristics of the organism, which include its novel genetic and phenotypic characteristics.

[49] See: http://bch.cbd.int/, accessed 15 May 2017.
[50] James C, (2016) Global status of Commercialized biotech/GM Crops: ISAAA Brief No. 52-2016.
[51] See: http://www.cera-gmc.org/gmcropdatabase.
[52] See: http://www.isaaa.org/gmapprovaldatabase/default.asp.
[53] See: http://www.isaaa.org/resources/infographics/gmapprovaldatabase/gm-approval-infographic-01.pdf.
[54] Global Industry Coalition, Views on the identification of living modified organisms may have an adverse effect on the conservation and sustainable use of biological diversity, 15 September 2009. Available at: http://bch.cbd.int/database/record.shtml?documentid=105780.
[55] Global Industry Coalition, Views on the identification of living modified organisms that are not likely to have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health, 30 April 2012. Available at: http://bch.cbd.int/database/record.shtml?documentid=105749.
[56] National Academy of Sciences (1987) Introduction of recombinant DNA-engineered organisms into the environment: key issues. National Academy Press, Washington DC.
[57] OECD (1986) Recombinant-DNA safety considerations. Organization for Economic Cooperation and Development, Paris.

In 2016, the Online Forum on Risk Assessment and Risk Management under the Cartagena Protocol held two discussions on synthetic biology: "*Submission of views, relevant guidance and sources of information on risk assessment of organisms developed through synthetic biology*" (9-23 May), and "*Possible considerations during the environmental risk assessment of LMOs developed or created through approaches commonly referred to as "synthetic biology"* (13-27 June)[58]. It was evident in these discussions that regulators with experience in assessing LMOs consider that existing risk assessment approaches are adequate for applications that may be considered "synthetic biology". Furthermore, these regulators were unable to identify a current or foreseeable LMO that presented novel risks or that could not be managed using existing approaches.

Potential challenges for LMO risk assessment that have been raised in synthetic biology discussions under the CBD include the availability of suitable comparators, and increasing uncertainty as a consequence of increasingly complex genetic modification. However, as we saw in the 2016 online discussions, concerns about comparators were not expressed by experienced risk assessors; many of whom noted they had not encountered problems in completing risk assessments. Similarly, the uncertainties mentioned in these discussions were hypothetical and not experienced in real world practice of risk assessments conducted to date. More recently, the US NAS undertook a review of the future products of biotechnology[59]. In their report, they conclude that irrespective of the degree of novelty and complexity of a potential product, the risk assessment end-points remain the same as these identified for existing biotechnology products, however the path to these end-points may be more diverse or complex.

It is generally accepted in the synthetic biology discussion under the CBD that the "products" of "synthetic biology" applications, and the "components" used in "synthetic biology" applications are non-living and therefore not in the scope of the Cartagena Protocol. Actual and potential non-living products that may be termed "synthetic biology" by some include a range of agricultural and industrial chemicals (e.g. biofuels, cosmetics), therapeutic goods, veterinary medicines, and food additives (e.g. flavouring). Such products are subject to a range of regulatory mechanisms, and fall within the scope of existing regulatory frameworks (where appropriate) covering their safe use (e.g.

[58] See: http://bch.cbd.int/onlineconferences/2014_2016period.shtml.
[59] NASSEM (National Academies of Sciences, Engineering, and Medicine) (2017) Preparing for the future products of biotechnology. Washington, DC. National Academies Press.

US Food and Drug Administration (FDA) GRAS[60], or EU Novel Food directive[61]) and trade. Regulation of chemicals is based on an assessment of the product's properties and not the process by which it was manufactured. As such, it is duplicative and unnecessary to consider the need for additional risk assessment requirements due to the use of a biological manufacturing process.

Components, sometimes referred to as genetic elements or "parts", that are used in, or derived from organisms developed in "synthetic biology" applications are also chemicals that are subject to a range of regulatory mechanisms (see Section E below). When an LMO is used in, or is the product of, a "synthetic biology" application, the components it contains will be assessed according to existing risk assessment approaches, consistent with Annex III, which requires consideration of the characteristics of modifications, including inserted nucleic acids and their functions. An often cited characteristic of "synthetic biology" applications (but not unique to it) is the use of "standard parts" with known functions[62] (see also: BioBrick® parts[63]; "What are BioBricks" [64]; iGEM[65]). Registries of "parts" exist that are collaboratively utilised[66] by research groups across the world. The use of standard parts[67], and adherence to established and validated protocols[68,69], along with transparent information sharing and recording of experimental outcomes from different laboratories allows for a body of knowledge to be established for each standard part over time. Therefore, a consequence of standardisation is a common understanding of the potential risks presented by certain components.

[60] See: https://www.fda.gov/food/ingredientspackaginglabeling/gras/.
[61] See: https://ec.europa.eu/food/safety/novel_food/legislation_en.
[62] E.g. iGEM parts registry: http://igem.org/Registry.
[63] See: BioBricks Foundation, https://biobricks.org/, site accessed May 23, 2017.
[64] See: What are BioBricks? NC State https://sites.google.com/a/ncsu.edu/biobricks-and-golden-gate-cloning/what-are-biobricks; accessed 23 May 2017.
[65] See: The international Genetically Engineered Machine (iGEM) competition,http://igem.org/Main_Page and http://parts.igem.org/Main_Page, accessed 23 May 2017.
[66] Silva-Rocha R, Martínez-García E, Calles B, Chavarría M, Arce-Rodríguez A, de Las Heras A, Páez-Espino AD, Durante-Rodríguez G, Kim J, Nikel PI, Platero R, de Lorenzo V (2013) The standard European vector architecture (SEVA): a coherent platform for the analysis and deployment of complex prokaryotic phenotypes, *Nucleic Acids Research* 41:D666–D675.
[67] Schaumberg KA, Antunes MS, Kassaw TK, Xu W, Zalewski CS, Medford JI, Prasad A (2016) Quantitative characterization of genetic parts and circuits for plant synthetic biology, *Nature Methods* 13:94–100.
[68] Patron NJ, Orzaez D, Marillonnet S, Warzecha H, Matthewman C, Youles M, Raitskin O, Leveau A, Farré G, Rogers C, Smith A, Hibberd J, Webb AA, Locke J, Schornack S, Ajioka J, Baulcombe DC, Zipfel C, Kamoun S, Jones JD, Kuhn H, Robatzek S, Van Esse HP, Sanders D, Oldroyd G, Martin C, Field R, O'Connor S, Fox S, Wulff B, Miller B, Breakspear A, Radhakrishnan G, Delaux PM, Loqué D, Granell A, Tissier A, Shih P, Brutnell TP, Quick WP, Rischer H, Fraser PD, Aharoni A, Raines C, South PF, Ané JM, Hamberger BR, Langdale J, Stougaard J, Bouwmeester H, Udvardi M, Murray JA, Ntoukakis V, Schäfer P, Denby K, Edwards KJ, Osbourn A, Haseloff J (2015) Standards for plant synthetic biology: a common syntax for exchange of DNA parts, *New Phytologist* 208:13–19.
[69] Vazquez-Vilar M, Quijano-Rubio A, Fernandez-del-Carmen A, Sarrion-Perdigones A, Ochoa-Fernandez R, Ziarsolo P, Blanca J, Granell A, Orzaez D (2017) GB3.0: a platform for plant bio-design that connects functional DNA elements with associated biological data, *Nucleic Acids Research* 45:2196-2209.

D. Examples of risk management and other measures that have been put in place to avoid or minimize the potential adverse effects of organisms, components and products of synthetic biology, including experiences of safe use and best practices for the safe handling of organisms developed through synthetic biology

Where a risk assessment identifies a risk of an adverse effect that is relevant to defined protection goals, a risk management strategy may be developed to minimize or mitigate this risk. We note in Section C above that the Cartagena Protocol requires the proportionate ("to the extent necessary"; see Article 16) imposition of measures to manage risks posed by an LMO, as identified by a risk assessment conducted according to Annex III. As also stated earlier, organisms resulting from certain "synthetic biology" applications are LMOs as defined by the Cartagena Protocol, and the risk assessment principles and methodologies of Annex III apply.

In practice, the types of risk management measures that have been implemented for releases of biotech crops into the environment have only been necessary in the early phases of testing and not for commercial releases. These measures range from confinement strategies and restrictions in use (e.g. small-scale release, physical controls such as greenhouses, fences, isolation distances, pollen traps), monitoring requirements such as monitoring zones and removal of volunteer plants, record keeping and reporting requirements, and contingency plans[70]. Post-commercial (unconfined) release measures have been used on a case-by-case basis, including the introduction of refuge areas, crop rotation, weed control, and reporting requirements. The EU, for example, requires of systematic literature reviews in annual post-market environmental monitoring of authorized GMOs[71] for the purpose of supporting evidence-based decision-making[72]. Examples of risk management measures can be found in the conditions for LMO field trial release imposed by competent authorities, or the conditions imposed by regulators for commercial releases of LMOs. Good examples to consult include the conditions of licenses granted by the Office of the Gene Technology Regulator (OGTR) in Australia[73], and the field trial requirements of permits issued by the United

[70] E.g. see Office of the Gene Technology Regulator, Risk Analysis Framework 2013.
[71] EFSA (European Food Safety Authority), Devos Y, Guajardo IM, Glanville J, Waigmann E (2017) Explanatory note on literature searching conducted in the context of GMO applications for (renewed) market authorization and annual post-market environmental monitoring reports on GMOs authorized in the EU market. EFSA supporting publications 2017:EN-1207. 48 pp.
[72] Kohl C, Frampton G, Sweet J, Spök A, Haddaway NR, Wilhelm R, Schiemann J (2015) Can systematic reviews inform GMO risk assessment and risk management? *Frontiers in Bioengineering and Biotechnology* 3:113.
[73] See: http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/ir-1.

States Department of Agriculture Animal and Plant Health Inspection Service (USDA-APHIS)[74], and the Canadian Food Inspection Agency (CFIA)[75]. The type of risk management measure(s) used should be the most appropriate to adequately address an identified risk. In the case of research and early development releases, risk management measures should also account for uncertainties, and a combination of measures may be used to ensure a sufficient level of management. The same approach applies to releases of LMOs resulting from "synthetic biology" applications.

Risk management measures should ideally be consistent, structured, non-discriminatory, predictable, open, transparent, evidence-based, legitimate, accountable, and, over time, subject to review[76]. The Cartagena Protocol is only one of a range of international, regional and national regulatory mechanisms that apply to biotechnology, and therefore to "synthetic biology", to assess and manage risks. These apply to LMOs, and when appropriate, to non-living products when used as components in "synthetic biology" applications. Examples for measures applicable to LMOs include the biosafety guidelines of the World Health Organization[77], the Centers for Disease Control and Prevention[78], and the US National Institute of Health[79]. These establish risk group classification levels for organisms that are assigned on the basis of risk assessment. While these are voluntary guidelines, they were developed from the 1970s and provided the foundation for regulation of the biosafety field and serve as models for the development of national regulatory frameworks which are well implemented[80]. These guidelines are also regularly reviewed and updated to ensure adequate coverage of new technological developments. Section E below details additional regulatory mechanisms that are relevant to managing the risks presented by LMOs.

In addition to risk management measures that may be imposed through formal regulation, there are other mechanisms that have been developed in order to ensure that biotech activities are conducted in a responsible way and to provide a form of risk management. These include voluntary and/or self-regulation that apply to the safe use of LMOs as well as components that may be used in

[74] See: https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/permits-notifications-petitions/SA_Permits.
[75] See: http://www.inspection.gc.ca/plants/plants-with-novel-traits/applicants/directive-dir2000-07/eng/1304474667559/1304474738697.
[76] See: The European Risk Forum, Principles of risk management. http://www.riskforum.eu/principles.html.
[77] World Health Organization, Laboratory Biosafety Manual (3rd ed, 2004).
[78] US Dept Health and Human Services, Centres for Disease Control and Prevention, National Institutes of Health – Biosafety in Microbiological and Biomedical Laboratories (5th ed, 2009).
[79] US Department Of Health And Human Services, National Institutes Of Health (2016) NIH Guidelines For Research Involving Recombinant Or Synthetic Nucleic Acid Molecules.
[80] Global Industry Coalition, Transit and Contained Use, 31 October 2016. Available at: https://croplife.org/plant-biotechnology/cartagena-protocol-on-biosafety/transit-and-contained-use/.

"synthetic biology" applications. For example, the work of researchers that belong to an institution (e.g. university), government laboratory or corporation will be subject to internal institutional/organizational biosafety, biosecurity and ethics reviews, and additional rules and procedures. A directly relevant example is the iGEM competition that has a Safety Committee and requires participants to observe safety rules spanning project design, laboratory safety, and shipping of components, policies that restrict certain "synthetic biology" applications, and the use of certain components and organisms[81]. These institutional requirements aim to ensure that the activities conducted are meeting the legal requirements for work with LMOs and other biosafety or biosecurity associated regulatory requirements. They also foster proactive and engaged self-evaluation by researchers, and promote awareness about potential issues.

Biotech researchers are required to comply with institutional/organizational codes of conduct, and examples exist that apply specifically to biotechnology/synthetic biology. One of these is the IAP Statement on Biosecurity (2005)[82] that was endorsed by 71 member scientific academies throughout the world engaging in responsible use of the technology and avoiding its misuse. Another example is the 2009 IASB Code of Conduct for Best Practices in Gene Synthesis (International Association of Synthetic Biology)[83] that recognises the need for safe and responsible use of synthetic nucleic acids, and implements screening of synthesis requests and customers, as well as reporting of suspicious or illegal activities. Similarly, the US Department of Energy Joint Genome Institute has a Synthetic Biology Internal Review procedure[84] for DNA synthesis proposals. The purpose of this review is to assess the broader aspects of the research and also to encourage researchers to more extensively consider environmental, biosafety, and biosecurity aspects of their project proposals.

Potential risks associated with LMOs and components used in "synthetic biology" raised in the synthetic biology work under the CBD include biosecurity and dual-use-of-concern. Here, the biosecurity guidelines of the World Health Organization[85] and the Centers for Disease Control and Prevention[86] are relevant to risk assessment and management. For example, the WHO guidelines comprises an overarching biorisk management approach that builds on existing biosafety guidelines, standards and norms to minimize or prevent the occurrence and consequences of human error

[81] See: http://2017.igem.org/Safety.
[82] See: http://www.interacademies.net/File.aspx?id=5401.
[83] See: http://op.bna.com.s3.amazonaws.com/hl.nsf/r%3FOpen%3djaqo-7xqpnr.
[84] See: http://jgi.doe.gov/user-program-info/community-science-program/synthetic-biology-guidelines/
[84] See: http://bch.cbd.int/synbio/open-ended/discussion_2014-2016.shtml.
[85] World Health Organization, Biorisk Management – Laboratory Biosecurity Guidance (2006).
[86] US Dept Health and Human Services, Centres for Disease Control and Prevention, National Institutes of Health – Biosafety in Microbiological and Biomedical Laboratories (5th ed, 2009).

within the laboratory environment. Aspects of this include establishing clear roles and responsibilities, promoting cultures of awareness and responsibility, and strengthened training, collaboration and emergency responses. Consistent with the WHO biosafety and biosecurity guidelines, the CEN[87] Workshop Agreement on Laboratory Biorisk Management Standard[88] developed by participants from 76 countries sets out a biorisk management system that complements ISO standards and is being transformed into an ISO standard itself.

There are also international treaties[89] relevant to biosecurity, and these are supported by international initiatives. One example is the Australia Group[90], which is an informal group of countries aiming to minimize the risk of chemical or biological weapon production via implementation of an export licensing system that controls transfers of certain biological agents, including components containing sequences associated with the pathogenicity of certain human, animal and plant pathogens. National programs exist also, one example is the Federal Select Agent Program[91] in the United States that oversees the possession, use and transfer of certain biological agents and toxins on the basis that they have the potential to pose a severe threat to public, animal or plant health or to animal or plant products. In addition, the US Department of Health and Human Services (DHHS) developed the "Screening Framework Guidance for Providers of Synthetic Double Stranded DNA" with the objective of minimizing the risk that unauthorized individuals or individuals with malicious intent will obtain "toxins and agents of concern" through the use of nucleic acid synthesis technologies, and to simultaneously minimize any negative impacts on the conduct of research and business operations[92].

The issues of biosecurity and dual-use –of-concern in the "synthetic biology" discussions under the CBD has included citizen science/the DIY community. Concerns about this community arise from the perception that enabling tools such as DNA synthesis and genome editing and the necessary laboratory equipment are affordable, accessible and easy to implement outside of traditional institutional/organizational laboratory settings. There is published literature assessing the

[87] European Committee for Standardization (CEN).
[88] Laboratory Biorisk Management Standard (CWA 15793:2011).
[89] Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction (Biological Weapons Convention); Protocol for the Prohibition of the Use in War of Asphyxiating, Poisonous or Other Gases, and of Bacteriological Methods of Warfare.
[90] See: http://australiagroup.net/en/index.html.
[91] See: https://www.selectagents.gov/index.html.
[92] Screening Framework Guidance for Providers of Synthetic Double-Stranded DNA (2010) *Federal Register*, Vol. 75, No. 197 2010. Available at: https://www.phe.gov/Preparedness/legal/guidance/syndna/Pages/default.aspx.

capabilities and capacities of this community that generally conclude that the expertise and technical skills of the DIY community are overstated, and that their activities require minimal biosafety precautions because these raise minimal biosafety concern[93,94]. The literature also highlights the proactive, collaborative and responsible culture of DIY communities in regard to biosafety[95]. This is demonstrated by the development of codes of conduct[96] and use of support from biosafety experts[97] by prominent groups such as DIYBio. The capabilities of the DIY community were also assessed by three Scientific Committees of the European Commission[98] and the US Presidential Commission for the Study of Bioethical Issues who concluded that their capacities and capabilities are limited, with a focus on education and knowledge sharing[99], and there is no need to impose unique limits on them[100].

The DIY community should be subject to the same regulatory mechanisms as other scientists working in biotechnology. These are predominantly implemented at the national level and are within the responsibility of the relevant competent authorities. The recent review of the future products of biotechnology by the US NAS[101] identified the existence of knowledge gaps with new entrants to the field, such as the non-traditional DYI community, in relation to understanding the regulatory system and the applicable regulations, and that it is necessary for regulatory agencies to address this. A recent demonstration of their extension into the DIY community is the communication by the Bavarian Health and Food Safety Authority[102] about the risk of exposure to several pathogenic bacteria associated with the use of a specific DIY bacterial gene engineering CRISPR kit manufactured by a US company[103]. This case was then assessed by the European Center for Disease Prevention and Control[104]. While the risks of people being infected by the contaminating

[93] Kuiken T (2016) Learn from DIY biologists, *Nature* 531:167-168.
[94] Ledford H (2015) Biohackers gear up for genome editing, *Nature* 524:398-399.
[95] Kuiken T (2016) Learn from DIY biologists, *Nature* 531:167-168.
[96] E.g. see: https://diybio.org/codes/.
[97] E.g. see: http://ask.diybio.org/.
[98] Scientific Committee on Health and Environmental Risks (SCHER); Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR); Scientific Committee on Consumer Safety (SCCS).
[99] European Union (2015) European Commission, DG Health and Food Safety – Scientific Committees on Health and Environmental Risks (SCHER); Emerging and Newly Identified Health Risks (SCENIHR); Consumer Safety (SCCS). Opinion on Synthetic Biology II - Risk assessment methodologies and safety aspects.
[100] Presidential Commission for the Study of Bioethical Issues (2010) New Directions – The ethics of synthetic biology and emerging technologies.
[101] NASSEM (National Academies of Sciences, Engineering, and Medicine) (2017) Preparing for the future products of biotechnology. Washington, DC. National Academies Press.
[102] Bavarian State Ministry of the Environment and Consumer Protection (2017) Potenzielle krankheitserreger im do-it-yourself-gentechnik-baukasten der firma The Odin.
http://www.lgl.bayern.de/presse/detailansicht.htm?tid=680089.
[103] See: http://www.the-odin.com/diy-crispr-kit/.
[104] European Centre for Disease Prevention and Control. Risk related to the use of 'do-it-yourself'

strains were determined to be low, it was recommended that suppliers of kits adhere to quality control procedures, with proper packaging, labelling, and documentation for the transport of biological materials consistent with applicable WHO guidelines[105].

The non-living products of synthetic biology include, for example, industrial chemicals (biofuels, cosmetics), agricultural chemicals, therapeutic goods, veterinary medicines, and food additives (flavours)[106]. All of these sectors have a complex range of long-established regulatory mechanisms for assessment and managing of risks, and these are discussed further in Section E below.

E. Regulations, policies and guidelines in place or under development which are directly relevant to synthetic biology.

An array of regulations, policies, guidelines, as well as self-regulation initiatives directly relevant to biotechnology and/or synthetic biology exist at regional, national and institutional levels. We disagree with assertions in synthetic biology discussions under the CBD that the absence of an overarching regulatory framework that covers all aspects of biotechnology/synthetic biology means existing regulation is inadequate. Different regulatory mechanisms will apply depending on the nature of the activity (e.g. research, field trial, commercial production), the type of product (e.g. LMO, chemical), and its intended use (e.g. contained use, environmental release, medical use), i.e. products that have applications in human or animal medicine, agricultural crop development and the production of biofuels will come under the scrutiny of different existing regulatory systems[107]. Some of these are detailed in Section D above as they relate to risk management. Listing all of the regulations, policies and guidelines that are directly relevant to "synthetic biology" is a substantial undertaking and beyond the scope of this submission. For the sake of brevity, and to provide an indication of the applicable regulatory complexity, in this section we provide an overview for two countries (United States and United Kingdom) and one region (European Union). These were selected because they were among the first in the world to examine these issues for synthetic biology, and they have substantial investment in "synthetic biology" (or industrial biotech) research.

CRISPR-associated gene engineering kit contaminated with pathogenic bacteria – 2 May 2017. ECDC, Stockholm.

[105] World Health Organization, Guidance on Regulations for the Transport of Infectious Substances (2015).

[106] OECD (2014) Emerging policy issues in synthetic biology. Organization for Economic Cooperation and Development, Paris.

[107] International Risk Governance Council, Geneva, (2010). Policy brief: Guidelines for the appropriate risk governance of synthetic biology. Available at: https://www.irgc.org/IMG/pdf/irgc_SB_final_07jan_web.pdf.

In addition, we would like to note the vast record in the BCH of examples of biosafety measures applied to LMOs by contracting parties and other governments.

In the US, "synthetic biology" is covered under relevant product-based and biotechnology regulations that were established at the federal level in the 1970s as recombinant DNA technology emerged, and have undergone a number of revisions since then. In the 1980s, when the first LMOs were advancing towards field testing, the federal government issued the trans-agency guidance document: "The Coordinated Framework", calling for regulation of LMOs via existing legal frameworks (established to manage non-biotech products). This approach differs to much of the rest of the world today, with its focus on case-by-case assessment of specific risks presented by the final product, rather than the process used to create it, and periodic review as technology and knowledge and understanding of risks develop. The federal agencies that regulate the use and commercial production of genetically engineered microbes and plants (LMOs), and foods and drugs (non-living products) include: EPA (pesticides/chemicals), US Department of Agriculture Animal and Plant Health Inspection Services (USDA APHIS – potential pathogens and plant pests, and veterinary biologics), and the FDA (food and drugs). Components used in "synthetic biology" applications, and LMOs used in/resulting from these may also be within the scope of the Select Agent Rules[108] of the Federal Select Agent Program[109] (see Section D) that is jointly administered by the Departments of Health and Human Services (HHS), the Centers for Disease Control and Prevention (CDC), and the USDA. Other federal agencies are concerned with safety standards in the workplace (Occupational Safety and Health Administration, OSHA), the interstate transport of hazardous materials, and export of infectious agents, knowledge or technologies (Department of Transportation, DOT; Department of Commerce, DOC). Overviews of the applicable US Federal regulations are presented in the report of the Presidential Commission for the Study of Bioethical Issues "New Directions – The Ethics of Synthetic Biology and Emerging Technologies"[110], the NSF Synthetic Biology Engineering Research Center (SynBERC)[111], and the 2017 NAS report on the Future Products of Biotechnology[112].

[108] See: https://www.selectagents.gov/regulations.html.
[109] See: https://www.selectagents.gov/index.html.
[110] Presidential Commission for the Study of Bioethical Issues (2010) New directions – the ethics of synthetic biology and emerging technologies.
[111] Bar-Yam S, Byers-Corbin J, Casagrande R, Eichler F, Lin A, Oesterreicher M, Regardh P, Turlington D, Oye K (2012) The regulation of synthetic biology: a guide to U.S. & European Union regulations, rules andguidellines, version 10. Available at:
https://www.synberc.org/sites/default/files/Concise%20Guide%20to%20Synbio%20Regulation%20OYE%20Jan%202012_0.pdf.
[112] NASSEM (National Academies of Sciences, Engineering, and Medicine) (2017) Preparing for the future products of biotechnology. Washington, DC. National Academies Press.

The work of "synthetic biology" researchers in the US is overseen by the NIH, with standards for the safe and ethical conduct of contained research provided by the "NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules" ("NIH Guidelines") [113]. The NIH Guidelines were originally established in 1976, and they are regularly updated (latest review in 2016), including a revision in 2013 to ensure adequate coverage of research with synthetic nucleic acids[114]. The NIH Guidelines are regarded as standards to be implemented by the research community as a whole, even though compliance is mandatory only for researchers receiving NIH funding. Often other government agencies, such as the Department of Energy, the Department of Veterans Affairs, and the USDA, require compliance with the NIH Guidelines as a condition of funding.

The policy issues surrounding synthetic biology in the United States were first examined in 2010 following the publication of the first self-replicating synthetic genome in a bacterial cell[115], with the report of the Presidential Commission for the Study of Bioethical Issues[116] concluding that there was no need to create additional agencies or oversight bodies focused specifically on synthetic biology, or new regulation or changes to existing regulation. Its report finds that in this application, the synthetic genome consisted of known sequences and gene functions and was a variant of the genome of an already existing species, and it was inserted into an already living host cell. This puts "synthetic biology" into perspective and challenges the notion of "creating life", which the Presidential Commission concludes remains remote for the foreseeable future. Their report also sets out ethical principles and recommendations that guide policy on emerging technologies, including, amongst others, investment in innovation for advancing public good, promoting a culture of responsibility in the synthetic biology community, proportionate regulatory oversight, and public engagement and education based on clear and accurate information.

Also in 2010, the National Science Advisory Board for Biosecurity (NSABB) released the report "Addressing Biosecurity Concerns Related to Synthetic Biology"[117]. The role of the NSABB is to

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[113] US Department of Health And Human Services, National Institutes Of Health (2016) NIH Guidelines For Research Involving Recombinant Or Synthetic Nucleic Acid Molecules (NIH Guidelines).
[114] See: http://osp.od.nih.gov/office-biotechnology-activities/biosafety/nih-guidelines.
[115] Gibson DG Glass JI, Lartigue C, Noskov VN, Chuang R-Y, Algire MA, Benders GA, Montague MG, Ma L, Moodie MM, Merryman C, Vashee S, Krishnakumar R, Assad-Garcia N, Andrews-Pfannkoch C, Denisova EA, Young L, Qi ZQ, Segall-Shapiro TH, Calvey CH, Parmar PP, Hutchison CA 3rd, Smith HO, Venter JC (2010) Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome, *Science* 329:52.
[116] See: https://bioethicsarchive.georgetown.edu/pcsbi/sites/default/files/PCSBI-Synthetic-Biology-Report-12.16.10_0.pdf.
[117] National Science Advisory Board for Biosecurity (April 2010) Addressing biosecurity concerns related to synthetic biology.

provide advice, guidance, and leadership regarding the oversight of dual use life sciences research. In their report they concluded that biosafety can be adequately addressed by the application of existing practices and procedures, in particular, current risk assessment frameworks. These reports were followed in 2012[118] and 2014[119] by US government policies concerning dual use of concern that again emphasize a culture of responsibility in the scientific community; these reports recognize that federal agencies can guide biosafety, biosecurity and ethical standards, however implementation relies on the scientific community in all areas of biological research.

The principles and recommendations of the Presidential Commission report are evident in policy developments in the UK. The release of "A Synthetic Biology Roadmap for the UK" in 2012[120] presented a vision for realizing the potential of synthetic biology by delivering a cutting edge synthetic biology sector that is economically vibrant, diverse and sustainable, and of clear public benefit. Core themes of the Roadmap include the need for responsible research and innovation, including the need for awareness, training, and adherence to regulatory frameworks. The Roadmap recognizes that regulation of the risks of "synthetic biology" is covered by existing relevant conventions and legislation, including the Cartagena Protocol, and EU and UK GMO legislation, and emphasizes that good practice in synthetic biology research requires a culture of responsibility, awareness and evaluation of risks, and proportionate regulation. In the same year, the Health and Safety Executive published "Synthetic Biology – A Review of the Technology, and Current and Future Needs from the Regulatory Framework in Great Britain"[121]. Its report also determined that the current UK GMO regulatory framework, with its risk assessment framework, adequately covers present and near future synthetic biology activities.

The 2012 Synthetic Biology Roadmap for the UK led directly to major public funding and policy activities, including the establishment of new synthetic biology research centers including the Innovation and Knowledge Centre (IKC) SynbiCITE[122], DNA synthesis facilities, training centers and a seed fund for innovative companies. In addition, the Synthetic Biology Leadership Council (SBLC)

[118] United States Government Policy for Overnight of Life Sciences Dual Use Research of Concern (Mar 2012) available at: https://www.phe.gov/s3/dualuse/Documents/us-policy-durc-032812.pdf.
[119] United States Government Policy for Institutional Overnight of Life Sciences Dual Use Research of Concern (Sept 2014) available at: https://www.phe.gov/s3/dualuse/Documents/oversight-durc.pdf.
[120] A Synthetic Biology Roadmap for the UK (2012) Published by Technology Strategy Board on behalf of UK Synthetic Biology Roadmap Coordination Group; available at: http://www.rcuk.ac.uk/documents/publications/syntheticbiologyroadmap-pdf/.
[121] Health and Safety Executive 2012. RR944 - Synthetic Biology: A Review of the Technology, and Current and Future Needs from the Regulatory Framework in Great Britain. Available at: http://www.hse.gov.uk/research/rrpdf/rr944.pdf.
[122] See: http://www.synbicite.com/about-us/.

was founded to manage the continued growth of this field. In 2016, the SBLC updated the Roadmap with the publication of the "UK Synthetic Biology Strategic Plan 2016 — Biodesign for the Bioeconomy"[123]. This plan builds on the recommendations of the Roadmap, and while it is focused on accelerating the translation of ideas into economic benefits, it again emphasizes the need for responsible innovation, which requires the engagement of a range of stakeholders, dialogue based on balanced and accurate information, and proportionate governance.

On the issue of dual-use-of-concern, policy developments in the UK were aimed at strengthening implementation of the Biological Weapons Convention[124]. Throughout the 2000s, the Royal Society, who is a member of IAP (see Section D) actively supported the development of codes of conduct in this area, and published a policy document in 2008[125]. Like the policy documents of the US government, the Royal Society emphasizes risk assessment, noting that the risk of misuse should be based on critical and realistic risk assessment and not exaggerated; openness and transparency, without censorship or prohibition of research simply because it is considered to be dual use; education and awareness raising, with a focus on the scientific community itself and how it communicates with the public; and the importance of codes of conduct for building cultures of responsibility. Similarly, in 2007 the Government Office for Science published "A Universal Ethical Code for Scientists"[126]. While this applies to all scientists, its aims include fostering ethical research, encouraging scientists to reflect on the implications and impacts of their work, and to support communication between scientists and the public.

In the EU, three Scientific Committees of the European Commission[127] concluded that a range of existing EU regulations for biological, chemical or genetic engineering research and products apply to "synthetic biology". In their "Opinion on Synthetic Biology I – Definition"[128], they provide an extensive list of references to applicable European legislation spanning a broad range of fields that may be relevant depending on the nature and uses of the product, including: GMO regulations; GMO

[123] SBLC (2016) Biodesign for the Bioeconomy: UK Synthetic Biology Strategic Plan 2016.
[124] Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction (Biological Weapons Convention).
[125] Royal Society Activities on Reducing the Risk of the Misuse of Scientific Research, RS Policy Document 17/08 (2008).
[126] Available at: https://www.liverpool.ac.uk/media/livacuk/researchintegrity/Government_Office_for_Science_Ethical_Code_for_Scientists.pdf.
[127] Scientific Committee on Health and Environmental Risks (SCHER); Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR); Scientific Committee on Consumer Safety (SCCS).
[128] European Commission Health & Consumers Directorate (2014) Opinion on Synthetic Biology I – Definition, http://ec.europa.eu/health/sites/health/files/scientific_committees/emerging/docs/scenihr_o_044.pdf assessed on 23 May 2017

medicinal products; biological risks; occupational health; new medicinal products; medical devices; gene therapy, cell therapy and tissue engineering; clinical trials; cosmetic products; chemicals; and products intended for food and feed uses. In particular, the safety and regulatory aspects for "synthetic biology" applications are considered in light of the current EU GMO regulatory framework.

At the international level, as noted above in Section D, the Cartagena Protocol applies to LMOs resulting from "synthetic biology", and additional international, regional and national regulatory mechanisms may also apply as appropriate. For activities with LMOs in containment these include the biosafety and biosecurity guidelines of the World Health Organization[129,130] and the Centers for Disease Control and Prevention[131]. For transport, including transboundary movements, the UN Recommendation on the Transport of Dangerous Goods ("Model Regulations") includes LMOs. The Model Regulations provide a scheme for the harmonized development of national and international regulations for all modes of transport (road, rail, marine, inland waterway, air), and they are translated into binding modal regulations[132].

The non-living products of "synthetic biology" applications may include chemicals, therapeutic goods, veterinary medicines, and food additives[133]. All of these sectors have a complex array of long-established regulatory mechanisms. For example, at the international level a cursory view reveals that several treaties apply to chemicals[134], along with international bodies[135], policy frameworks[136], recommendations and guidelines[137] and codes of conduct[138]. The OECD assessment of emerging policy issues in synthetic biology concluded that there is no need for entirely new

[129] World Health Organization, Laboratory Biosafety Manual (3rd ed, 2004).
[130] World Health Organization, Biorisk Management – Laboratory Biosecurity Guidance (2006).
[131] US Dept Health and Human Services, Centres for Disease Control and Prevention, National Institutes of Health – Biosafety in Microbiological and Biomedical Laboratories (5th ed, 2009).
[132] E.g. International Maritime Dangerous Good Code; Convention on International Civil Aviation; Convention Concerning International Carriage by Rail; European Agreement concerning the International Carriage of Dangerous Goods by Inland Waterways; European Agreement Concerning the International Carriage of Dangerous Goods by Road.
[133] OECD (2014) Emerging Policy Issues in Synthetic Biology (OECD Publishing).
[134] E.g. Stockholm Convention, Basel Convention, Rotterdam Convention, International Plant Protection Convention, Montreal Protocol.
[135] E.g. Inter-Organization Programme for the Sound Management of Chemicals, Codex Alimentarius, World Trade Organization, International Labor Organization.
[136] E.g. UNEP Strategic Approach to International Chemicals Management.
[137] E.g. UN Recommendation on the Transport of Dangerous Goods; UN Globally Harmonized System of Classification and Labelling of Chemicals.
[138] E.g. see: The International Code of Conduct on Pesticide Management. FAO, at: http://www.fao.org/agriculture/crops/thematic-sitemap/theme/pests/code/en/.

approaches where fossil-derived chemicals are replaced with bio-produced chemicals, as the existing regulatory systems remain adequate[139].

To conclude, the examples presented in this section illustrate that a range of existing regulations, policies and guidelines are applicable to "synthetic biology", in both CBD Parties (UK and EU) and a non-Party (US). In the UK and the US, technological advances have triggered reviews to examine whether current regulatory mechanisms remain appropriate and applicable. It is evident that to remain effective, regulations need to be periodically reviewed and revised to cover technological developments, as well as incorporate new understanding and knowledge of risks. It is also evident that while the multitude of regulations, polices and guidelines can direct biosafety, biosecurity and ethical conduct, much rests on implementation by the scientific community, and on individual scientists. This highlights the importance of the themes of the policy documents of the US and UK that emphasize a culture of responsibility, awareness and transparency. These examples also demonstrate that the existence of global regulatory frameworks do not necessarily impact on the development or implementation of regulatory mechanisms for biotechnology. A new international regulatory framework specifically for "synthetic biology" would only duplicate the mechanisms that already exist and remain relevant and applicable.

F. Knowledge, experience and perspectives of indigenous peoples and local communities in the context of living in harmony with nature for comparison and better understanding of the potential benefits and adverse effects of synthetic biology.

The GIC does not claim to represent indigenous peoples and local communities (IPLCs), but would like to take this opportunity to comment on relevant experiences with existing products of biotechnology that have been reported in the published literature. As we have established above, we consider "synthetic biology" to be part of the continuum of biotechnological development, and biotech crops are the products (LMOs) of biotechnology for which we have the most evidence of impacts. Also, as referred to above in Section C, CropLife International has a database containing published literature on the socio-economic and developing country benefits provided by biotech crops.[140] This literature reveals that biotech crops have been adopted by more than 18 million farmers in 30 countries throughout the world, with up to 90% of these farmers being

[139] OECD (2014) Emerging Policy Issues in Synthetic Biology. OECD Publishing.
[140] Available at: http://biotechbenefits.croplife.org/; accessed 26 May 2017.

smallholders[141]. Bt cotton is grown by more than 15 million smallholder farmers[142] and is the most studied of the biotech crops in this context. The literature shows that in developing countries, the adoption of Bt cotton has generated additional income for the small farm sector due to higher yields and reduced pesticide input costs, and employment for the landless rural poor, who rely on the labor market for their livelihood[143,144]. There is also evidence for improved farmer education[145] and improved economic status for women, who are often the most disadvantaged in rural societies[146]. Such studies indicate that the adoption of biotechnology can contribute to improving the welfare of smallholder farmers, and the broader goals[147] of decreasing poverty and more environmentally sustainable agricultural practices.

The GIC would also like to take this opportunity to express our views on issues that have been raised in this context – and not by IPLCs – in the synthetic biology work under the CBD. This work has generated robust debate about the impact of biotechnological developments on IPLCs, with a specific focus on hypothetical examples of how these developments could lead to negative impacts on income and loss of livelihood. While many of the elements in the CBD synthetic biology discussion are broadly applicable to LMOs (e.g. safety, ecological interactions), particular attention has been given to "synthetic biology" as an alternative production method of valuable chemicals that are currently derived from natural sources, with high profile examples including artemisinin and vanilla/vanillin. Microbial production of an artemisinin precursor in yeast (artemisinic acid) is considered to provide a relatively cost-effective, environmentally friendly, high-quality and reliable source of artemisinin[148]; however, this has been presented as a threat to farmers of the plant *Artemisia annua* which is the common source of the anti-malarial drug. Such claims fail to put the issue of potential impacts into perspective; artemisinin is an effective treatment for malaria, a disease that claims more than 500,000 lives each year, and biotech approaches for its production

[141] ISAAA (2016) Global status of commercialised biotech/GM crops: 2016, ISAAA Brief No. 52.
[142] Bukitbayeva S, Qaim M, Swinnen J (2016) A black (white) hole in the global spread of GM cotton, *Trends in Biotechnology* 34:260-263.
[143] See: Vitale J, Vognan G, Vitale PP (2016) The socio-economic impacts of GM cotton in Burkina Faso: does farm structure affect how benefits are distributed? *AgBioForum* 19:120-135, and references within.
[144] Chakraborty K (2010) The economics of BT cotton production in India – a meta analysis, *Indian Journal of Economics and Business* 9(4).
[145] Ibid.
[146] Kouser S, Abedullah, Qaim M (2017) Bt cotton and employment effects for female agricultural laborers in Pakistan, *New Biotechnology* 34:40-46.
[147] E.g. Millennium Development Goals: http://www.unmillenniumproject.org/goals/.
[148] Hale V, Keasling JD, Renninger N, Diagana TT (2007) Microbially derived artemisin: a biotechnology solution to the global problem of access to affordable anti-malarial drugs, *American Journal of Tropical Medicien and Hygiene* 77:198-202.

were developed to supplement erratic agricultural supply[149]. There was an extended debate about vanilla/vanillin in the 2015 Online Forum on Synthetic Biology[150], which has been shown to be based on inaccurate and highly speculative information. Vanillin[151] produced by engineered yeast is a different product for a different market than vanilla cultivated from vanilla orchid pods by farmers, and it competes with other synthetic vanillin products, of which the majority are derived from a petrochemical[152].

The examples discussed here highlight the importance of carefully considering the accuracy and relevance of information contributed to synthetic biology work under the CBD. Further, the notion that naturally sourcing products is more consistent with the objectives of the CBD can also be challenged[153]. For example, other agricultural production methods for vanilla plants are being researched in order to meet quality and quantity demands that also reduce land use[154]. Moreover, despite the existence of various sets of recommendations for the conservation and sustainable use of medicinal and wild plants[155], only a small portion of these resources have achieved adequate protection, for example via conventional conservation in natural reserves or botanic gardens[156]. We also point out that the potential economic impacts due to technological developments would be better addressed in forums other than the CBD as product displacement may occur due to a range of circumstances that go beyond biotechnological applications.

[149] Paddon CJ, Keasling JD (2014) Semi-synthetic artemisinin: a model for the use of synthetic biology in pharmaceutical development, *Nature Reviews Microbiology* 12: 355-367.
[150] See: http://bch.cbd.int/synbio/open-ended/discussion_2014-2016.shtml.
[151] Gallage NJ, Møller BL (2015) Vanillin–bioconversion and bioengineering of the most popular plant flavor and its de novo biosynthesis in the vanilla orchid, *Molecular Plant* 8: 40-57.
[152] Waltz E (2015) Engineers of scent, *Nature Biotechnology* 33:329-332.
[153] Mujtaba Shah G, Abbasi AM, Khan N, Guo X, Ajab Khan M, Hussain M, Bibi S, Nazir A, Ahmad Tahir A (2014) Traditional uses of medicinal plants against malarial disease by the tribal communities of Lesser Himalayas–Pakistan, *Journal of Ethnopharmacology* 155:450-462.
[154] Tan BC, Chin CF, Alderson P (2010) Optimisation of plantlet regeneration from leaf and nodal derived callus of *Vanilla planifolia* Andrews, *Plant Cell Tissue and Organ Culture* 105:457-463.
[155] See: http://www.floraweb.de/map-pro/.
[156] Chen S-L, Yu H, Luo H-M, Wu Q, Li C-F, Steinmetz A (2016) Conservation and sustainable use of medicinal plants: problems, progress, and prospects, *Chinese Medicine* 11:37.

Appendix I: Selected literature describing the experience and benefits

of biotechnology-derived crops (2010-2016)

1. CAS-TWAS CoEBio (2016) Biotechnology: A Growing Field in the Developing World. Clarivate Analytics: Available at: http://english.im.cas.cn/ns/es/201611/W020161115403490152491.pdf.

2. Mabubu JI, Nawaz M, Hongxia H (2016) Advances of transgenic Bt-crops in insect pest management: An overview, *Journal of Entomology and Zoology Studies* 4:48-52.

3. US NASEM (2016) Genetically Engineered Crops: Experiences and Prospects (2016) National Academy Press, Washington DC. Available at: https://www.nap.edu/catalog/23395/genetically-engineered-crops-experiences-and-prospects.

4. Brookes G, Barfoot P (2016) GM crops: global socio-economic and environmental impacts 1996-2014. PG Economics Ltd, UK.

5. UK Council for Science and Technology (2014) GM Science Update. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/292174/cst-14-634a-gm-science-update.pdf.

6. Smyth SJ, Kerr WA, Phillips PWB (2015) Global economic, environmental and health benefits from GM crop adoption, *Global Food Security* 7:24-29. doi: 10.1016/ j.gfs.2015.10.002.

7. Kljumper W, Qaim M (2014) A meta-analysis of the impacts of genetically modified crops, *PloS ONE* 9:e111629. doi: 10.1371/journal.pone.0111629.

8. Carpenter JE (2013) The socio-economic impacts of currently commercialized genetically engineered crops, *International Journal of Biotechnology* 12:249-268. doi: 10.1504/ijbt.2013.059248.

9. Ayobami AS, Valesca A, Vidal BF, Vasco A (2013) Biotechnology and agriculture, *Journal of Biosafety and Health Education* 1:2. doi: 10.4172/jbhe.1000103.

10. Mannion AM, Morse S (2012) Biotechnology in agriculture: agronomic and environmental considerations and reflections based on 15 years of GM crops, *Progress in Physical Geography* 36:747-763.

11. Juma C (2012) Technological abundance for global agriculture: the role of biotechnology (March 1, 2012). HKS Working Paper No. RWP12-008. Available at SSRN: https://ssrn.com/abstract=2020447 or http://dx.doi.org/10.2139/ssrn.2020447.

12. Green JM (2012) The benefits of herbicide-resistant crops, *Pest Management Science* 68:1323-1331. doi: 10.1002/ps.3374.

13. Karthikeyan A, Valarmathi R, Nandini S, Nandhakumar MR (2012) Genetically modified crops: insect resistance, *Biotechnology* 11:119-126. doi: 10.3293/biotech.2012.119.126.

14. Commission on Genetic Resources for Food and Agriculture (2011) Agriculture biotechnologies in developing countries: Options and opportunities in crops, forestry, livestock, fisheries and agro-industry to face the challenges of food insecurity and climate change. CGRFA 13/11/Inf.8 Commission on Genetic Resources for the Food and Agriculture Organization, Rome.

15. Ronald P, Rine J (2011) Plant genetics, sustainable agriculture and global food security, *Genetics* 188:11-20.

16. Franke AC, Beukers MLH, Broer W, Bunte FHJ, Dolstra O, Engelbronner-Kolff FMd', Lotz LAP, Montfort J, Nikoloyuk J, Rutten MM, Smulders MJM, Wiel CCM van de, Zijl M (2011) Sustainability of current GM crop cultivation: review of people, planet, profit effects of agricultural production of GM crops, based on the cases of soybean, maize, and cotton. Plant Research International report 386. Wageningen UR.

17. Sanahuja G, Banakar R, Twyman RM, Capell T, Christou P (2011) *Bacillus thuringiensis*: a century of research, development and commercial applications, *Plant Biotechnology Journal* 9:283-300.

18. Carpenter JE (2011) Impacts of GM crops on biodiversity, *GM Crops* 2:1-17.

19. Park JR, Mcfarlane E, Phipps RH, Graziano Ceddia M (2010) The role of transgenic crops in sustainable development, *Plant Biotechnology Journal* 9:2-21. doi: 10.1111/j.1467-7652.2010.00565.

20. Food and Agriculture International Conference Technical Paper (2010) Agricultural biotechnology for food security and sustainable development: options and priorities for action by the international community. ABDC-10/9 Food and Agriculture Organization, Rome.

21. Qaim M (2010) Benefits of genetically modified crops for the poor: household income, nutrition, and health, *New Biotechnology* 27:552-557.

22. Paarlberg R (2010) GMO foods and crops: Africa's choice, *New Biotechnology* 27:609-613.

23. Cominelli E, Tonelli C (2010) Transgenic crops coping with water scarcity, *New Biotechnology* 27:473-477.

Appendix II: Selected literature demonstrating experience with risk assessment (2012 - 2016)

1. Brookes G, Barfoot P (2016) GM crops: global socio-economic and environmental impacts 1996-2014. PG Economics Ltd, UK.

2. National Academy of Sciences (2016) Publisher: National Academies of Sciences, Engineering, and Medicine. p. 606 DOI: https://doi.org/10.17226/23395.

3. Yaqoob H, Shahid AA, Samiullah TR, Rao AQ, Khan MA, Tahir S, Mirza SA, Husnain T (2016) Risk assessment of Bt crops on the non-target plant-associated insects and soil organisms, *Journal of the Science of Food and Agriculture*96:2613-2619 doi: 10.1002/jsfa.7661.

4. Zheng-jun G, Shun-bao L, Zheng-Ping G, Biao L, Wei W (2016) Do genetically modified plants affect adversely on soil microbial communities? *Agriculture, Ecosystems and Environment* 235:289-305. doi.org/10.1016/j.agee.2016.10.026.

5. Aldemita RR, Reaño IM, Solis RO, Hautea RA (2015) Trends in global approvals of biotech crops (1992–2014), *GM Crops Food* 6:150-166. doi: 10.1080/21645698.2015.1056972.

6. Casacuberta JM, Devos Y, du Jardin P, Ramon M, Vaucheret H, Nogué F (2015) Biotechnological uses of RNAi in plants: risk assessment considerations, *Trends in Biotechnology* 33: 145–47. doi:10.1016/j.tibtech.2014.12.003.

7. Koch MS, Ward JM, Levine SL, Baum JA, Vicini JL, Hammond BG (2015) The food and environmental safety of Bt crops, *Frontiers in Plant Science* 6:283. doi: 10.3389/fpls.2015.00283.

8. Roberts A, Finardi-Filho F, Hegde S, Kiekebusch J, Klimpel G, Krieger M, Lema MA, Macdonald P, Nari C, Rubinstein C, Slutsky B, Vicien Cl (2015) Proposed criteria for identifying GE crop plants that pose a low or negligible risk to the environment under conditions of low-level presence in seed, *Transgenic Research* 24(5), Springer International Publishing: 783–90. doi:10.1007/s11248-015-9899-z.

9. Singh D and Mathew IL (2015) The effect of *Bacillus thuringiensis* and Bt transgenics on parasitoids during biological control, *International Journal of Pure and App. Bioscience* 3:123-131.

10. CERA (2014) Low-level presence in seed : a science based approach to expedited environmental risk assessment, http://www.cera-gmc.org/files/cera/uploads/era_llp_in_seed_workshop_proceedings_2014.pdf.

11. Dubelman S, Fischer J, Zapata F, Huizinga K, Jiang C, Uffman J, Levine S, Carson D (2014) Environmental fate or double-stranded RNA in agricultural soils, *PLoS ONE* 9:e93155 doi.10.1371/journal.pone.0093155.

12. Garcia-Alonso M, Hendley P, Bigler F, Mayeregger E, Parker R, Rubinstein C, Satorre E, Solari F, McLean M (2014) Transportability of confined field trial data for environmental risk assessment of genetically engineered plants: a conceptual framework, *Transgenic Research* doi:10.1007/s11248-014-9785-0.

13. Roberts A, Devos Y, Raybould A, Bigelow P, Gray A (2014) Environmental risk assessment of GE plants under low-exposure conditions, *Transgenic Research* 23:971–83. doi:10.1007/s11248-013-9762-z.

14. Carstens K, Cayabyab B, De Schrijver A, Gadaleta PG, Hellmich RL, Romeis J, Storer N, Valicente FH, Wach M (2013) Surrogate species selection for assessing potential adverse environmental impacts of genetically engineered insect-resistant plants on non-target organisms, *GM Crops and Food* 5(1) Taylor & Francis: 11–15. doi:10.4161/gmcr.26560.

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