Comment for the Convention on Biological Diversity's Substantive Body on Scientific, Technical and Technological Advice (SBSTTA) in response to Conference of the Parties (CoP) Decision XII/24: New and emerging issues: synthetic biology

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The risk analysis challenge of synthetic biology for the SBSTTA

The Institute for Agriculture and Trade Policy (IATP) appreciates the opportunity afforded by CoP Decision XII/24 to comment on the consequence for the CBD of Living Modified Organisms (LMOs) derived from current synthetic biology techniques, per Articles 8g) and 19.[i] An LMO is "any biological entity capable of transferring or replicating genetic materials, including sterile organisms, viruses and viroids" (Article 3h), Cartagena Protocol on Biosafety). Because LMOs "derived from current synthetic biology techniques fall under the Cartagena Protocol on Biosafety," Parties to the CBD and the Protocol are required, and non-Party governments are urged to take measures to regulate and control at the national level environmental risks that could have "adverse effects on the conservation and sustainable use of biological diversity."[ii]

Some anticipated uses of synthetic biology are likely to result in environmental release of synthetic LMOs, not due to technical imperatives, but to lower the cost of producing synthetic LMOs, e.g. for biofuel production in open algae ponds.[iii] For example, "Synthetic biology could also be used to modify plants that could then be used as feedstocks for biofuels, e.g. ethanol production. Product developers would engineer the plant to lower the amount of unfermentable material in the plant or to alter the plant material so that it is easier to turn into fuel. APHIS [U.S. Department of Agriculture's Animal and Plant Health Inspection Service] has already issued permits for fields trials of plants with these properties."[iv]

The CBD Secretariat overview of areas of research under the synthetic biology rubric comprehends and indeed, exceeds, much of what IATP knows of the various techniques of synthetic biology.[v] In our view, the cross border transmission of digital information derived from genetic resources for subsequent "booting up" in a cell culture is tantamount to the transboundary movement of LMOs, since such digital genetic information has no functional independence or purpose apart from its role in expressing LMO traits.[vi] Thus synthetic biology practice, even if partly digital, is within the jurisdiction of the Protocol's provisions concerning the transboundary movement of LMOs.

The following remarks are directed with reference to the CBD and the Protocol, rather than to the relevance of other international legal instruments to synthetic biology, as reviewed in the Secretariat paper.[vii] The international standards setting bodies referenced in the World Trade Organization agreements have yet to write standards that apply to products derived from synthetic biology, so it would be premature to speculate on how, when or whether trade-related sanitary and phyto-sanitary rules will be applied to international traded synthetic biology products and

components. However, the intensive patenting of synthetic biology applications and the breadth of patent claims is such that the CoP is well-advised to continue to evaluate whether and which synthetic biology applications and products may fall under Article 27 on excluding from patentability "essential biological processes" in the WTO Trade Related Intellectual Property Rights Agreement (TRIPs).[viii]

Whether synthetic biology products and components are developed through intensive patent regimes or through an open-source process of licensing biological parts for use, [ix] a crucial regulatory problem confronts the CoP: as noted by the International Civil Society Working Group on Synthetic Biology[x], the Protocol's Annex III on risk assessment is inadequate to evaluate synthetic LMOs that have no comparator in nature.[xi] Therefore, the risk assessment and risk management of synthetic biology must no longer rely on the legal concept of "substantial equivalence" between a GMO and its conventional comparator, which was used to deregulate GMOs in the 1990s and continues to do so.[xii] In its comments on the European Food Safety Authority's draft guidance, TestBiotech notes that,

> The approach of comparative risk assessment is very much influenced by the DNA centered paradigm of the last century that tries to predict effects in the cell or in organisms and even on the level of ecosystems on the basis of genomic structures. Many of the risks and effects that can be expected in this context are far beyond what can be investigated on the level of the DNA or its products. In the light of recent knowledge about cell biology, including epigenetic, epistatis and pleiotrophic effects (none of them are mentioned in this draft [European Food Safety Authority] Guidance) and in awareness of many genome x environment interactions, the reductionist model of comparative assessment is no longer adequate.[xiii]

The SBSTTA revision of Annex III must not only be remove the genetic determinism paradigm that served as a core scientific principle of the "substantial equivalence" framework: it must treat risk analysis holistically. SBSTTA should ensure that a revision of Annex III establishes the risk management of synthetic biology as an independent authority, and not the rubber stamp of a scientifically outdated risk assessment model.

We are pleased to learn that "some Parties are already using the Guidance [on Risk Assessment of Living Modified Organisms] for the purpose of conducting risk assessments."[xiv] IATP looks forward to the proposed revision of the Guidance that will take into account "Risk assessment of living modified organisms produced through synthetic biology."[xv] We hope that this short contribution will aid that revision.

Learning from the history of classical genetic engineering

IATP's main focus on synthetic biology has been on the agricultural and food applications in the context of an inadequate regulatory environment in the U.S.[xvi] This relatively small focus, however, is informed by a broader background in the history of classical genetic engineering, particularly its risk assessment.

The Executive Secretary paper ably summarizes the foundation of the debate over the extent of the novelty of synthetic biology, insofar as "Synthetic biology applications use many of the techniques that are extensions of classical genetic engineering aided by greater computer power."[xvii]

The intent of these techniques is to make biological processes become more predictable in terms of the traits expressed and to standardize the biological parts expressing those traits.

We believe that the debate over the definition of synthetic biology should be informed by the history of science about classical genetic engineering.[xviii] The central dogma of molecular biology, writes Barry Commoner, "assumes that an organism's genome-its total complement of DNA genes--should fully account for its characteristic assemblage of inherited traits."[xix] However, the results of the Human Genome Project showed that "there are far too few human genes to account for the complexity of our inherited traits or for the vast inherited differences between plants, say, and people."[xx] What had been dismissed as "junk DNA," because it didn't fit into the genetic determinism of the central dogma, is now the object of high throughput sequencing and data mining.[xxi] But even as we learn more about the "junk," are we in danger of replacing the genetic determinism of molecular biology with a synthetic biology engineering determinism? The history of science and the ecology of biological diversity might be able to give the SBSTTA better guidance about what risks are presented by the environmental release of synthetic LMOs and whether those risks can be assessed and managed.

Since Dr. Commoner's prescient article, epigenetic studies have shown that DNA sequences have an unreliable predictive capacity for the determination of cellular traits and functions.[xxii] In revising the Protocol's Annex III on risk assessment, the SBSTTA should be well advised by epigenetic studies, lest it be swayed by those who minimize the risks posed to biodiversity because of the purported predictability and containment of traits resulting from the "engineering" of biological processes.

An operational definition of synthetic biology for the revised Annex III of the Protocol should not incorporate the claims or intentions of synthetic biologists, e.g. "Synthetic biology is an engineering discipline—there is a desire to build things that do not yet exist."[xxiii] Instead, a definition should include "the use of synthetic nucleic acids, however they are synthesized and whether in they result in products or their components."

Challenges to establishing an effective synthetic biology regulatory regime: lessons from the history of the environmental release of LMOs

IATP was involved in the negotiations of both the Convention on Biological Diversity and the Cartagena Protocol on Biosafety. We helped develop a proposal on liability and redress for damage resulting from the transboundary movement of genetically modified organisms.[xxiv] IATP has advocated for the implementation of the CBD and the Protocol in the United States, partly in response to the circumvention of the CBD by the United States via its trade and investment policy, and non-Party status to the Protocol.[xxv] Prior to and since the ratification of the Protocol, the U.S. government has provided commercial diplomatic support to companies that export LMOs internationally. This support includes lobbying for Monsanto in foreign countries after its conviction under the Foreign Corrupt Practices Act for bribing an Indonesian official to weaken or repeal an environmental rule governing the planting of LMOs.[xxvi]

An analysis of 926 Wiki-leaked cables from 2005-2009 of the U.S. Department of State's "science diplomacy" by Food and Water Watch, "reveals a concerted strategy to promote agricultural biotechnology overseas, compel countries to import biotech crops and foods that they do not want and lobby foreign governments—especially in the developing world—to adapt policies to pave the way to cultivate biotech crops."[xxvii] Notwithstanding the huge increase in pesticide use on

LMOs[xxviii], the millions of hectares of glyphosate resistance super-weeds[xxix], and the yield drag of some LMO crop varieties[xxx], the State Department has continued its commercial diplomacy on behalf of transboundary trade of LMOs. It is likely that the State Department will continue that commercial diplomacy on behalf of products derived from plant synthetic biology. As the SBSTTA revises the Annex III guidance on risks assessment and risk management of environmentally released synthetic LMOs, it should consider historical lessons from the environmental release of LMOs prior to the advent of plant synthetic biology.

In 2012, IATP was among 117 organizations that endorsed seven "Principles for the Oversight of Synthetic Biology," that outlined the normative objectives of oversight, e.g. "No synthetic organism or their synthetic building blocks should be commercialized or released without full disclosure to the public of the nature of the synthetic organism and the results of safety testing."[xxxi] Regrettably, the Principles have failed to achieve their objectives. For example, unregulated commercial products derived from synthetic biology techniques are now on grocery store shelves,[xxxii] though not without protest.[xxxiii]

Nevertheless, the CoP Decision on synthetic biology could play an important role in alerting Parties and non-Party governments about synthetic biology applications, methodology, trading practices and/or policies that may impede the conservation and sustainable use of biological resources, as well as access to and benefit sharing from the use of biological resources. (We believe that the potential for synthetic biology to contribute to the conservation of individual biological resources, e.g. through enabling nitrogen fixation in non-legumes, and thus reducing the water and soil impacts of chemical fertilizers, is too uncertain and premature to merit a SBSTTA discussion."[xxxiv])

IATP supports the CoP decision to reiterate the CBD's advocacy of a precautionary approach and more specifically its objective that Parties and government non-Parties "establish or have in place, effective risk assessment and management procedures and/or regulatory systems to regulate environmental release of any organism, components or products resulting from synthetic biology techniques, consistent with Article 3 of the Convention" (paragraph 3a, Decision). The key term in this objective is "effective."

It is possible to have a legal framework in place to regulate the environmental release of synthetic LMOs but decline to apply that law out of concern, e.g. that an Environmental Impact Statement (EIS) would result in undue delay of a product into commerce. Furthermore, an EIS may be required, as in the United States, but the results of that EIS cannot provide "any additional legal basis for denying a permit based on adverse environmental impacts revealed in the EIS."[xxxv] It is insufficient for Parties and non-Party governments to "establish or have in place" regulatory systems to prevent damage to biological diversity from the environmental release of synthetic LMOs: the systems must be used and enforced.

Finally, to have an effective regulatory regime, the biosafety data submitted by commercial applicants for synthetic LMOs must be available for peer review. If governments routinely allow biosafety data to be classified as Confidential Business Information, the regulatory review of that data will be less robust. The usual reason proffered for CBI classification is unconvincing: "as patents provide exclusive rights for commercial use, most trait and event-specific data on composition, environmental interactions, allergenicity, toxicity and other safety aspects are of limited commercial utility to non-patent holders. Moreover, such biosafety information cannot be used meaningfully for illegal product copying."[xxxvi] A revised Annex III to the Protocol must stipulate the granting of CBI status to biosafety data and information will be exceptional and only upon

demonstration that making public biosafety data will result in commercial advantage for a specific competitor regarding the biosafety data submitted as part of a regulatory application for commercialization.

Great expectations and the investment pressure to avoid the effective regulatory regime required by Article 3 of the CBD

Professor Claire Marris has written, "Compared to GM crops, scientific and governmental institutions have employed strategies to deal with public concerns earlier in the development of the field of synthetic biology."[xxxvii] Because governments are major investors in synthetic biology[xxxviii] and these investment funds come largely from taxpayers, it is understandable that governments and the scientific institutions they fund wish to explain to the public the benefits or potential benefits of what the public is funding, albeit often in public private partnerships in which the public investment is privatized and monopolize via the patent system. However, government public engagement strategies not only come with lessons, learned or not, about earlier public engagement on the relatively few applications of transgenic modification of row crops. Government strategies for synthetic biology come with investment expectations of product commercialization that may prove to be quite unrealistic and difficult to manage.

As one administrator of U.S. government synthetic biology investments noted, "Our basic understanding of biology is still very limited. All of the expectations about synthetic biology have frankly not been able to be met in the time frame that investors would have liked. Our basic understanding of even a single cell to grow and propagate is in its infancy. We are trying in a very short time to overcome 2 billion years of programming by nature."[xxxix] Synthetic biologists seek to derive and combine standardized biological parts to make them perform predictably according to principles of engineering. The limitations of synthetic biology's understanding about the cellular environments of genetic information, to say nothing of the much more complex resistance of biological diversity to its reduction to a sum of engineered parts, may frustrate those governments among the CoP who hope to create myriad products and global markets derived from synthetic biology by expediting commercialization through 'light touch' regulation or industry self-regulation.

It would be tragic if this frustration blinded governments and scientific institutions to other applications of science, technology and traditional knowledge that might realize the objectives of the CBD and Protocol more effectively, at lower cost and with fewer risks. As the CoP considers existing and potential impacts of synthetic biology applications on the realization of the objectives of the CBD and the Protocol, IATP believes it should do so in the context of comparative technology assessment and investment for the realization of those objectives. Such comparative technology assessment would not be a comparative study of synthetic biology assessments to develop a synthetic biology narrative both to attract funding and manage investor expectations[xl]—however useful such comparative studies may be to investors—but a comparison of technological applications for achieving a given purpose.

Because of the large investments and hopes placed in synthetic biology, the structure of public dialogue about it often has been predicated on an unhappy synergy of very great expectations and equally great, if not greater, fears that the great expectations will fail to be realized. For the fearful, failure would be ascribed not to the limitations of the underlying science or specific applications of engineering biology, but to scientifically illiterate opposition to the promise of synthetic biology.

For example, well in advance of commercially viable products derived from synthetic biology, a report from the United Kingdom's Royal Academy of Engineering stated:

> Synthetic biology is destined to become of critical importance to building the nation's wealth. It has the potential to transform world industry in areas such as energy, health and the environment; to produce a new era of wealth generation; and create large numbers of new jobs.[xli]

Such a manifest of destiny for synthetic biology may pre-commit governments, in practice if not in policy, to avoid everything that might impair or delay the hoped for benefits. For example, the European biotechnology industry has gone to great lengths to demonstrate why specific SMO techniques should not be subject to regulations governing the risk assessment and commercialization of GMOs. A briefing paper for European policy makers by the New Breeding Technologies Platform provides an elaborate legal taxonomy of post-transgenic modification techniques to justify why they should not be regulated under EU laws as genetically modified organisms (GMOs).[xlii] This strategy has been strongly criticized: "Industry demands to exclude synthetic gene technologies from the EU regulations must be resisted. Allowing the release of relevant plants, insects or animals without safety assessment and systematic monitoring and labelling of the resulting products would be irresponsible. On the contrary, risk assessment has to be strengthened to comply case by case with the complexity of the risks posed by of the new techniques."[xliii] However, governments eager to see their investments in synthetic biology result in commercial products may opt for a regulatory regime based in voluntary data submission and without pre-market safety assessment, post-market monitoring and labeling.

An evaluation of targeted gene modification (TagMo) technologies, sometimes grouped under synthetic biology, notes "TagMo might also be used to introduce foreign genes [into plants] without using traditional DNA recombinant techniques. As a result, TagMo might fall outside existing US and EU regulatory definitions and scrutiny."[xliv] A regulatory decision by a Party or a non-Party government that a particularly technique is not governed by existing regulations should not inhibit a SBSTTA Decision about what kinds of synthetic biology techniques need to be regulated effectively to achieve the objectives of the Convention and the Protocol.

Environmental release of SMOs: a commercial inevitability?

Light touch regulation could include, e.g. a lack of environmental risk assessment for synthetic LMOs intended for environmental release. U.S. Environmental Protection Agency (EPA) regulators are struggling to determine which techniques of synthetic biology fall under their current legislative authority from 1967 and regulatory authority from 1997 for microbial organisms. Since most of the techniques and applications of synthetic biology have been developed over the past decade, EPA regulators believe that many applications fall outside of their authority.[xlv]

The most evident concern regarding open field trials with synthetic LMOs is whether various barriers proposed to prevent horizontal gene transfer (HGT) will work. There is some consensus that more than one kill switch will have to be built in to synthetic LMOs to prevent HGT. "However," notes a group of biosafety researchers, "the higher the complexity of a safety device, the more prone it may be to disturbance and failure."[xlvi] The term "disturbance" here may be understood in the sense of electronic like circuitry: too many gene circuit devices in a SMO may result in "disturbance" of the complex of redundant devices designed to prevent HGT.

If the "kill switches" or other barriers do not prevent HGT, the consequences for biological diversity are difficult to foresee. Much biosafety work in synthetic biology is predicated on the economic likelihood of the synthetically modified organism release in open environments: e.g." Economic viability of some of these applications, such as biofuels, may require the intentional release of synthetically engineered organisms into the environment, often on a massive scale."[xlvii] Operating on this assumption, the goal of organizing dialogue and scientific cooperation between synthetic biologists and ecologists is not to discuss the consequences of the environmental release of synthetic LMOs for biological diversity and its sustainable use, but to realize "the aim of developing an environmentally benign organisms."[xlviii] In structure and purpose, such dialogues are reactive to the products and processes of synthetic biology applications whose high risks for biodiversity are implicitly justified by presumed high rewards.[xlix] But who will benefit from the cultivation of synthetic LMOs in open fields? That question is worthy of a high level discussion in the CoP.

The Secretariats request for information on synthetic biology does not include consideration of liability and redress for damage to biologically diversity. However, liability and redress are germane to the "socioeconomic impacts relevant to the mandate of the Convention and its Protocols." It is likely that the commercialization of synthetic LMOs developed for biofuels feedstocks and other agro-industrial uses would place onerous liability provisions on farmers for contamination of non-SMO crops and/or alleged patent violations. Current technology use agreements absolve the commercial developer of GMOs from any liability for HGT and subsequent loss of organic or conventional crop certification.[l] Assuming that GMO purveyors will employ the same legal strategy for shifting synthetic LMO engendered liability to farmers for HGT, there is no legal barrier, at least in the United States, to inhibit the outcrossing of synthetic LMOs to wild or agricultural plants.

Conclusion

While this comment does not address all of the questions to be discussed by the Ad Hoc Technical Working Group (AHTEG) on Synthetic Biology, as it advises the SBSTTA, IATP believes it is vital to lay the groundwork to encourage a more robust international debate on appropriate regulations of this evolving technology. We hope that the information and viewpoints provided here will assist the AHTEG in its vital work.

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[i] "Possible Gaps and Overlaps with the Applicable Provisions of the Convention, Its Protocol and Other Relevant Agreements Related to Components, Organisms and Products Resulting from Synthetic Biology Techniques," Convention on Biological Diversity, 12th Conference of the Parties, UNEP/CBD/COP/INF/12, September 29, 2014, paragraph 6.

[ii] Ibid., paragraphs 6-7.

[iii] Michael Ferry, Jeff Hasty and Natalie Cookson, "Synthetic Biology Approaches to Biofuels Production," *Biofuels* (2012) 3(1) at 10. http://biodynamics.ucsd.edu/pubs/articles/Ferry12.pdf

[iv] Ibid., 22.

[v] "Potential Positive and Negative Impacts . . . "Executive summary, paragraph 2.

[vi] With reference to the question implied in "Possible Gaps and Overlaps," paragraph 11. We acknowledge that "many countries do not apply the Cartagena Protocol's provisions on risk assessment and the minimum

required information to naked DNA and its constituent parts be because they are considered to be components rather than products of LMO." ("Possible Overlaps and Gaps," paragraph 75).

[vii] "Possible Gaps and Overlaps . . ."

[viii] "Possible Gaps and Overlaps . . ." paragraphs 215-237.

[ix] Bryn Nelson, "Synthetic Biology: Cultural Divide," *Nature*, May 7, 2014. http://www.nature.com/news/synthetic-biology-cultural-divide-1.15149

[x] The International Civil Society Working Group on Synthetic Biology (ICSWGSB) "A Submission to the Convention on Biological Diversity's Subsidiary Body on Scientific, Technical and Technological Advice (SBSTTA) on the Potential Impacts of Synthetic Biology on the Conservation and Sustainable Use of Biodiversity," October 17, 2011. https://www.cbd.int/doc/emerging-issues/Int-Civil-Soc-WG-Synthetic-Biology-2011-013-en.pdf

[xi] "Possible Gaps and Overlaps . . ." paragraph 108.

[xii] Christopher Then, "Testbiotech analysis of EFSA [European Food Safety Authority] Guidance on the environmental risk assessment of genetically modified plants," Testbiotech, December 21, 2010, 3. https://www.testbiotech.org/sites/default/files/Testbiotech_comment_on_EFSA_%20Guidance_ERA.pdf

[xiii] Then, "Testbiotech comment on EFSA´s draft Guidance for environmental risk assessment of genetically engineered animals," August 2012. https://www.testbiotech.org/sites/default/files/Testbiotech%20Comment%20on%20ERA%20of%20GE%20animals.pdf

[xiv] "Report of the Ad Hoc Technical Expert Group On Risk Assessment And Risk Management Under The Cartagena Protocol On Biosafety," June 10, 2014. paragraph 18, http://www.cbd.int/doc/meetings/bs/bsrarm-05/official/bsrarm-05-06-en.pdf

[xv] Ibid., paragraph 38 h).

[xvi] Steve Suppan, "From GMO to SMO: How Synthetic Biology Evades Regulation," Institute for Agriculture and Trade Policy, July 2014. http://www.iatp.org/files/2014_07_18_Synbio_SS_0.pdf

[xvii] "Potential Positive and Negative Impacts of Components, Organisms and Products Resulting from Synthetic Biology Techniques on the Conservation and Sustainable Use of Biodiversity and Associated Social, Ecnomic and Cultural Considerations," Conference of the Parties to the Convention on Biological Diversity, UNEP/CBD/COP/12/INF11, September 24, 2014, paragraph 21.

[xviii] E.g. Pablo Pellegrini, "Anomalies in the early stages of plant transgenesis: interests and interpretations surrounding the first transgenic plants," tr. Catherine Jagoe, *Historia, Ciencias, Saude—Maguinhos*, Vol. 20, October-December 2013. http://www.scielo.br/pdf/hcsm/v20n4/en_0104-5970-hcsm-20-04-01453.pdf

[xix] Barry Commoner, "Unraveling the DNA Myth: The Spurious Foundation of Genetic Engineering," *Harpers*, February 2002. http://www.artsci.wustl.edu/~anthro/articles/Commoner%20UNRAVELING%20THE%20DNA%20MYTH%20Feb02.htm

[xx] Ibid.

[xxi] Stephen S. Hall, "Hidden Treasures in Junk DNA," *Scientific American*, September 18, 2012. http://www.scientificamerican.com/article/hidden-treasures-in-junk-dna/

[xxii] ICSWGSB, "Submission," 16-18.

[xxiii] Christopher Voigt cited in "Realizing the potential of synthetic biology," *Nature Reviews: Molecular Cell Biology*, Vol. 15, April 2014, 290.

[xxiv] E.g., Gurdial Singh Nijar, Kristin Dawkins and Neil Sorenson, "Developing a Liability and Redress Regime Under the Cartagena Protocol on Biosafety," Institute for Agriculture and Trade Policy, 2000. http://www.iatp.org/files/Developing_a_Liability_and_Redress_Regime_unde.pdf ; Kristin Dawkins, "Report from Cartagena: The Sad Story of the Failed Biosafety Negotiations," Institute for Agriculture and Trade Policy, March 1999. http://www.iatp.org/files/Sad_Story_of_the_Failed_Biosafety_Negotiations.htm

[xxv] E.g., Kristin Dawkins et al, "Letter to U.S. Secretary of State Madeleine Albright," June 30, 1997. http://www.iatp.org/files/Letter_to_Madeleine_Albright,_Secretary_of_Sta.htm ; Kristin Dawkins, Rod Leonard et al, "Sign On Letter to Vice President Al Gore About the Biosafety Protocol," December 21, 1998. http://www.iatp.org/documents/sign-on-letter-to-al-gore-about-the-biosafety-protocol-122198 Kristin Dawkins et al, "Letter to President William Clinton," November 17, 1999. http://www.iatp.org/files/Letter_to_President_Clinton_on_WTOs_TRIPs_Agre.htm Kristin Dawkins, "Next Skirmish in the 'Battle Royale of the 21st Century: Montpellier, France," Institute for Agriculture and Trade Policy, October 2000. http://www.iatp.org/files/Next_Skirmish_in_the_Battle_Royale_of_the_21st.htm

[xxvi] "Biotech Ambassadors: How the U.S. State Department Promotes the Seed Industry's Global Agenda," Food and Water Watch, May 2013, at 8-9. http://www.foodandwaterwatch.org/reports/biotech-ambassadors/

[xxvii] "Biotech Ambassadors," at 3.

[xxviii] E.g. Charles Benbrook, "Impacts of genetically engineered crops in the U.S. – the first 16 years," *Environmental Sciences Europe*, 2012. http://www.enveurope.com/content/24/1/24

[xxix] "International Survey of Herbicide Resistant Weeds," April 15, 2015. http://weedscience.org/

[xxx] Doug Gurian Sherman, "Failure to Yield: Evaluating the Performance of Genetically Engineered Crops," Union of Concerned Scientists, 2009. http://www.ucsusa.org/sites/default/files/legacy/assets/documents/food_and_agriculture/failure-to-yield.pdf

[xxxi] "Principles for the Oversight of Synthetic Biology," March 2012, at 5. http://libcloud.s3.amazonaws.com/93/ae/9/2287/2/Principles_for_the_oversight_of_synthetic_biology.pdf

[xxxii] Jaydee Hanson, "Synthetic Biology: Rebranding Extreme Genetic Engineering," Center for Food Safety, May 5, 2014 http://www.centerforfoodsafety.org/blog/3126/synthetic-biology-rebranding-extreme-genetic-engineering and Stephanie Storm, "Biofuel Tools Applies to Household Soaps, *The New York Times*, May 30, 2014. http://www.nytimes.com/2014/05/31/business/biofuel-tools-applied-to-household-soaps.html?hp&_r=0

[xxxiii] "Open letter to Ecover/Method," June 2, 2014. http://www.etcgroup.org/content/open-letter-ecover-method IATP is a signatory.

[xxxiv] Kent Redford et al, "How will synthetic biology and conservation shape the future of nature?" Wildlife Conservation Society, March 2013, at 4.

[xxxv] Sarah R. Carter et al., "Synthetic Biology and the U.S. Biotechnology Regulatory System: Challenges and Options," J. Craig Venter Institute, May 2014, 19. http://www.jcvi.org/cms/fileadmin/site/research/projects/synthetic-biology-and-the-us-regulatory-system/full-report.pdf

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[xxxvii] Claire Marris, "The Construction of Imaginaries of the Public As a Threat to Synthetic Biology," *Science As Culture*, 2014, at 13. http://dx.doi.org/10.1080/09505431.2014.986320

[xxxviii] Nancy J. Kelley et al, "Engineering Biology To Address Global Problems: Synthetic Biology Markets, Needs and Applications," *Industrial Biotechnology*, June 2014. DOI : 10.1089/ind.2014.1515

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[xli] Cited in Marris, "The Construction of Imaginaries of the Public As a Threat to Synthetic Biology," at 2.

[xlii] The regulatory status of plants resulting from New Breeding Technologies," NBT Platform, April 9, 2014.

[xliii] Then, "Synthetic gene technologies and their application regarding plants and animals in agriculture," TestBiotech, January 22, 2015, at 11. http://www.testbiotech.org/sites/default/files/Testbiotech_Factsheet_Synthetic_Gene_Technologies.pdf

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[xlv] Mark Segal, "EPA Oversight of Synthetic Biology," presentation to the National Academy of Sciences, October 24, 2013.http://sites.nationalacademies.org/cs/groups/pgasite/documents/webpage/pga_086096.pdf

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[xlvii] K. Drinkwater et al., "Creating A Research Agenda for the Ecological Implications of Synthetic Biology," Massachusetts Institute of Technology Program on Emerging Technologies and the Woodrow Wilson International Studies Center, May 7, 2014 at 7.

[xlviii] Ibid., at 8.

[xlix] Ibid., at 4.

[l] "Seed Giants vs. U.S. Farmers," Center for Food Safety and Seed Savers, 2013, at 25. http://www.centerforfoodsafety.org/reports/1770/seed-giants-vs-us-farmers