Results of the public consultation on SCENIHR's preliminary Opinion on the Synthetic Biology – Research Priorities

A public consultation on this Opinion was opened on the website of the non-food scientific committees between 16 July and 16 September 2015. Information about the public consultation was broadly communicated to national authorities, international organisations and other stakeholders.

12 organisations and individuals (contributing 61 comments in all) participated in the public consultation, providing input to different chapters and subchapters of the opinion. Among the organisations participating in the consultation were universities, institutes of public health, NGOs and public authorities.

Each contribution was carefully considered by the Working Group and the scientific Opinion has been revised to take account of relevant comments.

The Scientific Committees thank all contributors for their comments and for the references provided during the public consultation.

The table below shows all comments received on different chapters of the Opinion and SCENIHR's response to them. It is also indicated if the comment resulted in a change of the Opinion or if it did not.

Comments received during the public consultation on the SCENIHR preliminary opinion on "Synthetic Biology – Research priorities"

SUBMISSIONS				SCENIHR's response
No.	**Name of individual/organisation**	**Table of contents to which comment refers**	**Comments**	**SCENIHR's response**
1	Westra Jaco, RIVM - (National Institute for Public Health and the Envorinment, jaco.westra@rivm.nl, Netherlands	ABSTRACT	We thank the SCENIHR for their hard work in finalizing the third part of the opinion on synthetic biology. In this preliminary opinion on Synthetic Biology part III the SCENIHR addresses and identifies the major gaps in knowledge to be considered for performing a reliable risk assessment. The SCENIHR also provides recommendations for research needed to fill the identified gaps. On the whole we support the gaps and research needs identified by the SCENIHR. They are however rather general in nature, and specifics and details need to be clarified further when the research questions are operationalized. We also support the SCENIHR in their observation that their analyses is only applicable to the foreseeable future, and that periodical review is necessary.	A discussion on "specifics and details" is provided below in response to individual issues raised. We thank the commenter for these views, which we have taken into careful consideration. We have included the specific points and details raised in the relevant sections below in our discussion.
2	EuropaBIO, d.carron@europabio.org, Belgium	ABSTRACT	General comments EuropaBio calls for a balanced use of the research priorities in Opinion III. For example: The European Risk Forum's Innovation Principle states that whenever policy or regulatory decisions are under consideration, the impact on innovation should also be fully assessed and addressed. The research priorities recommended in EU Opinion III on Synthetic Biology should therefore be reviewed by policy makers considering both the need to protect society and the environment while also protecting Europe's ability to innovate In general, the structure and the priorities of the document were not clear to our members. In our view there should be a greater differentiation between deliberate release and contained use. We believe it is important to begin this document with the previously agreed definition of synthetic biology, namely: Synthetic Biology is the application of science, technology and engineering to	A reference, by direct quotation, of the definition of Synthetic Biology, as proposed in the first of this series of Opinions would be useful. Although it was included on page 11, line 7 of the preliminary Opinion, it has now been emphasised. The Opinion refers to present gaps in knowledge and risk assessment in the near-term future. This is stated in the Opinion and defined the scope of the analysis: there is no restriction of the analysis to either contained use or deliberate release. The SCs would like to refer readers to Opinion I for a discussion on the

			facilitate and accelerate the design, manufacture and/or modification of genetic materials in living organisms. This is particularly important since if Synthetic Biology is not defined and no consistent wording is used (possibly leading to confusion between synthetic biology with genetic engineering/modification), it may be wrongly perceived that additional legislation on already well regulated areas under GM-legislation is needed. Therefore clear distinction between GMMs, GMOs and synthetic biology is needed. Moreover we believe that references to socio-economic, ethical and social issues should not be included in this document.	relationship between GM and SynBio. Research priorities cannot be defined out of context, which includes "references to socio-economic, ethical and social issues". We agree that the analysis of research priorities takes place in a broader context, including social, governance, ethical, and security implications. The text was edited and these references remain in the document.
3	Paton Michael, Health & Safety Executive, michael.paton@hse.gsi.gov.uk, United Kingdom	ABSTRACT	Page 5, Line 13 …identifies major gaps in knowledge to be considered for performing a reliable risk assessment…. Comment: It would be helpful to clarify whether this comment applies to existing synthetic biology activities or more likely those that are planned in the next 10 years. Similarly does this refer to synthetic biology activities in contained use or deliberate release into the environment?	The Opinion refers to present gaps in knowledge and risk assessment in the near-term future. This is stated in the Opinion and defined the scope of the analysis: there is no restriction of the analysis to either contained use or deliberate release.
4	Fears Robin, EASAC (European Academies Science Advisory Council), robin.fears@easac.eu, United Kingdom	EXECUTIVE SUMMARY	EASAC welcomes the opportunity to contribute to this phase of the consultation and also reaffirms support for the transparent, interactive and inclusive process that has been used by the European Commission to generate and review the Scientific Committees' Opinion during the past year. Various points relevant to this part 3 of the consultation have already been discussed in the EASAC responses to parts 1 and 2 and in the source documents cited previously (in particular the EASAC report 2010 and the InterAcademy Partnership, IAP statement 2014). We note also that there are other documents appearing more recently that are relevant to parts 1 and 2 of the Opinion, we mention several of these in this response. We do not now repeat at length points we made in our earlier responses but will reiterate one key conclusion: we view synthetic biology as a continuous scientific development from fields such as biotechnology, nanotechnology, molecular and cellular biology rather than as a science arising independently from these fields. Therefore, it is probable that in the foreseeable future (regarded in the consultation as <10 years), the main synthetic biology developments are covered in the already available legislation and risk assessment that is embedded within the current procedures for GMOs, biotechnology, laboratory health and safety, and sector-specific product	This view is largely in line with the view expressed in the SynBio Opinions of the SCs.

			authorisation. In producing this response, EASAC has consulted with members of its Biosciences Steering Panel and with other experts nominated by individual academies and IAP.	
5	Cannell Martin, Defra, martin.cannell@defra.gsi.gov.uk, United Kingdom	EXECUTIVE SUMMARY	Page 7, Line 13 The current Opinion addresses specific risks to the environment from SynBio organisms, processes and products, partly in the context of Decision XI/11 of the Convention of Biodiversity, identifies major gaps in knowledge to be considered for performing a reliable risk assessment and provides research recommendations resulting from gaps identified. The use of 'major' could be taken to suggest that current risk assessment practices are not adequate. Suggest 'potential' instead of 'major'	The SCs suggest that the risk assessment practises are adequate, but there may be some gaps that will need to be reviewed in the future. We agree that distinguishing major and minor gaps is not helpful and have thus, removed these terms from the text.
			Page 7, Line 26: Bioenergy, agricultural and chemical industry applications of SynBio might drive significant land-use change towards feedstock production which may have negative impacts on biodiversity and conservation, e.g., through increased extraction of biomass from agricultural land resulting in decreased soil fertility or through extraction of biomass from the natural environment. The examples of risks outlined above are generic rather than specific risks. It should be mentioned that specific risks related to conservation and biodiversity will be addressed as part of the authorization process for release.	Risk management and regulatory processes, such as the authorization process for release are not within the scope of this Opinion.
			Page 7, Line 29: 'Negative impacts could also ensue from accidental releases' Yes definitely, but this sentence is leading because it implies that the risks of such negative impacts are somehow greater than existing risks from GMOs under contained use. This is unlikely to be the case, because containment measures will always be proportionate to the level of hazard posed by the work being undertaken.	The logic of this assessment is not quite clear. There is a lack of evidence to support the idea that "containment measures will always be proportionate to the level of hazard posed"; Although this is the aspiration, there is no guarantee that this will be the case, especially because determining the level of hazard is fraught with uncertainties.

			Page 7, Line 30: SynBio produces varieties of organisms, including de-extincted species, and products could destabilise conservation efforts and diminish support for conservation due to reduced focus on species and habitat preservation. It is worth mentioning that no de-extinct organism that could "destabilise conservation efforts and diminish support for conservation due to reduced focus on species and habitat preservation" is expected to be produced for many years	A main point here is that there is an on-going discussion about the prospect of de-extinction in the long-term future, which might have a negative impact on current conservation efforts. The text was adapted to make this clear.
			Page 7, Line 43: In general, risks are related to the emergence of new and uncharacterised biological functions, properties and products, and the absence of appropriate comparator organisms for the risk assessment. The absence of a comparator has no relationship with the level of risk present. Suggested alternative text: "...the absence of appropriate comparators means that alternative approaches to risk assessment may be required."	We agree with this comment and have added alternative text to the final document.
			Page 8, Line 1: With respect to citizen science, the probability of unintentional harm might increase because more people are starting to actively work with biological material. It would be helpful to qualify what is meant by "more people" in this context. Suggested alternative text: "…more people are starting to work with biological materials outside of conventional laboratory and institutional settings."	We agree with this comment and have clarified the text accordingly.
6	Scott Deborah, "Engineering Life" project, University of Edinburgh, Deborah.Scott@ed.ac.uk, United Kingdom	EXECUTIVE SUMMARY	p7 lines 16-18 I understand that the mandate of the SCs does not include "social, governance, ethical, and security implications," but to talk about processes such as risk assessment is to talk about social institutions and protocols. To talk about "safety by design" is also to talk about the governance of biosafety. This is not to say that the document should be stripped of these aspects – it is impossible to talk about environmental impacts and even just the practice of synthetic biology without also talking about these social, "non-technical" aspects. As it stands, the danger is that, because the document does touch on social and governance (and even ethics and security) in various ways, it ends up standing in for fuller discussions on those aspects. It might	We agree that the analysis of research priorities takes place in a broader context, including social, governance, ethical, and security implications. The text was edited as suggested.

			be more accurate to therefore state: "Outside the scope of the current mandates are specific, thorough analyses of social, governance, ethical, and security implications…"	
7	Scott Deborah, Engineering Life project, University of Edinburgh, Deborah.Scott@ed.ac.uk, United Kingdom	EXECUTIVE SUMMARY	p11 lines 15-21 The preliminary opinion rightly notes that SynBio "promises substantial benefits." However, in the next sentence, these promises have become simply "the benefits of SynBio," which are paired with "scientific uncertainties" and the development of the science "and their potential impact on the environment, the conservation and sustainable use of biological diversity, and human health." This framing of "benefits and uncertainties" is problematic – it makes it seem as though potential negative impacts are still uncertain but the potential benefits are known. At this point, most of the stated benefits of synthetic biology are still promissory statements, fraught with many uncertainties, both technical (whether the promised scientific developments will unfold as hoped) and much broader (whether the promised societal, environmental, economic etc benefits will occur). I would recommend consistently referring to "promised benefits," and explicitly including them under the "uncertainties" associated with synthetic biology.	This is a valid point and the text was changed accordingly.
8	Scott Deborah, Engineering Life project, University of Edinburgh, Deborah.Scott@ed.ac.uk, United Kingdom	EXECUTIVE SUMMARY	p14 line 11 – an Ad Hoc Technical Expert Group has been established, and will meet the week of 21 September 2015.	We corrected this point in the text.
			p14 lines 12-15 In addition to environmental release and field trials, Decision XII/24 also calls for: (para 3c) scientific assessments regarding potential effects on the conservation and sustainable use of biodiversity, addressing other issues such as food security and socioeconomic considerations as appropriate; and (para 3d) funding for research into synbio risk assessment methodologies, and to promote interdisciplinary research that includes related socioeconomic considerations; …which both seem relevant to the mandate of this paper.	We agree with this comment and have changed and expanded the text to address this point.
9	Jerala Roman, National institute of chemistry, Ljubljana, roman.jerala@ki.si, Slovenia	EXECUTIVE SUMMARY	This opinion is dominated by synthetic biology based on bacteria and synthetic systems (protocells). However the area of synthetic biology that has not been treated in this Opinion are medical applications of synbio, particularly based on engineered human cells. This is a very important area as it in fact already being applied and is much more advanced	Therapeutic applications of SynBio techniques were largely excluded from our analysis, because they were outside of our remit, and following from the explicit exclusion of human genetic engineering from GMO definitions.

			in this respect than e.g. protocells. Successes in medical applications will likely strongly impact the public perception of the benefits (or dangers) of synthetic biology. An example of medical application of synthetic biology is immunotherapy such as engineering T-cells from patents with CARs(chimeric antigen receptors) that target those engineered cells agains cancer cells and possible reengineering of cell signaling pathways for synthetic immunology. This is also an area of high investment, particularly in the USA but not so much in Europe. Currently those therapies are applied to patients that are nonresponsive to any other therapies with some spectacular results. Therefore the dangers of those therapies are not so relevant as for example for the treatment of healthy individiuals as e.g. for vaccines. However potential dangers, not so much for the environment as for the patient's health are present and represent an important scientific gap. Currently the existing kill switches for mammalian cells are not adequate and need to be developed but would also be applicable to therapies using stem cells. Also the methods of genime engineering of regulation such as CRISPR/Cas represent an extremely important tool whose potentials and risks need to be established and improved.	This aspect of SynBio and its risks are outside the scope of the mandate, which tasks us with assessing "specific risks to the environment". Moreover, the SCs did not focus on this type of therapeutic application, because the SCs think that it has a low impact on human health and environment. Therapeutic applications involving the use of such medicinal GMO (viral vectors and/or genetically modified human cells) are subject to a specific environmental risk assessment according to the provision of the GMO Directives. In this sense, it is expected that most of the 'medical applications of synthetic biology' will undergo existing risk assessment methodologies currently used under the GMO regulation for the foreseeable future. Therapeutic applications using engineered human cells will mostly have low impact on human health or the environment.
10	Sanders Dale, John Innes Centre, Dale.Sanders@jic.ac.uk, United Kingdom	EXECUTIVE SUMMARY	RESPONSE FROM THE JOHN INNES CENTRE The John Innes Centre (JIC) is an independent, international centre of excellence in plant and microbial sciences, based on the Norwich Research Park, UK. Research at the John Innes Centre makes use of a wide range of disciplines in biological and chemical sciences, including synthetic biology. We have a unique historical perspective on genetic research and its application to horticulture, agriculture and industrial biotechnology. We have played a key role in the development of GM, not only in the improvement of gene transfer techniques but also in studying genetically modified plants in glasshouse and field trials. The majority of John Innes Centre funding is won in open competition from funding agencies worldwide, with more than 50% coming from UK government sources. JIC is highly active in both plant and microbial synthetic biology. Large scale	The SCs thank you for your comment. No edits required.

			programmes include the UK research council funded Synthetic Biology Research Centre, OpenPlant, a collaborative initiative between the John Innes Centre and The Sainsbury Laboratory in Norwich and the University of Cambridge to develop tools for plant synthetic biology (www.openplant.org); the Gates Foundation funded Engineering Nitrogen Symbiosis for Africa programme (www.ensa.ac.uk); and the Biotechnology Resources for Arable Crop Transformation (BRACT; www.bract.org) programme to address safety issues surrounding GM crops and develop methodology for detection of possible unanticipated consequences of transgene insertion. JIC is represented annually in the international Genetically Engineered Machine (iGEM) competition by the JIC-Cambridge team and involvement in the NRP-UEA team, and provides world-class synthetic biology training and networking for early stage researchers, e.g. through the 2014 OpenPlant-ERASynBio summer school. In general, we found this a comprehensive and interesting document which highlights some of the challenges faced when trying to manage activities within this emerging field of science. We have submitted specific comments in the sections to which they are most relevant.	
11	EuropaBio, d.carron@europabio.org, Belgium	EXECUTIVE SUMMARY	P7, line 16-18 This draft opinion of the scientific committees should deal with risk assessment and it is explicitly stated that "outside the scope of the current mandate are the social, governance, ethical and security implications of Syn Bio" (page 7; line 16-18); however, all over the text there are ample references to socio-economical, ethical and societal issues, which we would suggest to delete.	We agree that the analysis of research priorities takes place in a broader context, including social, governance, ethical, and security implications. The text was edited.
			P7, line 23-24 "Key areas of applications of SB that might affect the objectives of the CBD". Comment: it is not clear from the text of this opinion, as well as from the previous opinion II, why these 6 areas have been identified as particularly related to the objectives of the CBD.	The identification of these Key areas is presented and explained in detail in Opinion I.

			P7, line 24-25 "They further analysed impacts on the so-called Aichi Biodiversity Targets for the 2011-2020 period" Comment: the stated scope for the present opinion makes it hard to understand how the Aichi targets can be addressed by the SCs.	The analysis of the potential impact of SynBio on the Aichi targets, within the stated scope of the Opinion, is detailed in Table 1 of the Opinion.
			P7, line 25-26 Recommended edit: delete "significant" as it is exaggerated as well as speculative in that it is not substantiated by any real life examples in the opinion.	Deleting "significant" would distort the message of the sentence, which deals with potentialities, not realities.
			P7, line 25-29 Suggested edit: "Bioenergy, agricultural and chemical industry applications of SynBio might drive land-use change towards feedstock production. Negative impact on biodiversity and conservation might be caused if excessive/unsustainable amounts of biomass are extracted from agricultural lands which could lead to soil fertility decrease or impacts the natural environment." (reference WWF studies on advanced bioethanol production http://awsassets.panda.org/downloads/wwf_smart_use_final_version.pdf)	The SCs consider the word significantly appropriate and have not edited this sentence.
			P7, line 29-33 "SynBio produces varieties of organisms, including de-extincted species" –this has not happened yet, and research into de-extinction is today very speculative and clearly beyond the timeframe that the SCs have indicated in their opinion of 2020. Suggested edit: delete sentence lines 30-32 "Negative impacts could also ….diminish support for conservation due to reduced focus on species and habitat preservation.	This argument does not depend on the existence of de-extincted species; the mere prospect of possible de-extinction could have the impact described. The text was adapted to make this clear.
			P8, line 4-6 "Many new approaches…further reduce environmental and health risk" Comment: It needs to be recognised clearly in the text that new approaches, etc. are needed in cases where likelihood exists that the organism, process or product developed with SynBio might cause harm, instead of a general statement that concerns the whole field of synthetic biology. We also believe that the word 'biotechnology' should be deleted as this applies to all approaches including classical breeding Suggested edit: "New approaches may be necessary, such as new forms of	The SCs would not like to reduce the scope of this recommendation, because it is not always possible to establish risks at an early stage. The SCs aimed for a precautionary approach. Details can be found in section 3.1.5 as well as in Opinion II.

			biocontainment and new biocontainment strategies to manage environmental and health risks where such risks are identified for a particular SynBio outcome."	
12	EuropaBio, d.carron@europabio.org, Belgium	EXECUTIVE SUMMARY	P8, line 26-29 "The use of genome editing methods in a multiplexed fashion allows the simultaneous generation of large number of variants, the genome-wide modification of organisms and a more pervasive change to the genomes of living organisms than those obtained by traditional genetic modification techniques. This might create additional challenges for risk assessment." Comment: the statement in the first sentence is factually wrong. Chemical and radiation mutagenesis, cell fusion and in vitro tissue culture, to cite but a few, are all established methods for genetic modification that result in large, simultaneous and pervasive changes in the genome of the treated organisms. These however, have not challenged the risk assessment of the resulting final organisms. Suggested edit: "The use of genome editing methods in a multiplexed fashion theoretically will allow the simultaneous generation of large number of variants, the genome-wide modification of organisms and a pervasive change to the genomes of living organisms comparable to the outcome of other mutagenesis techniques with established history of safe use. Possible challenges for risk assessment can be overcome by understanding better the mutation potential of genome editing tools."	The SCs edited this text, which now reads: "traditional targeted genetic modification techniques", to clarify that the Opinion does not consider random mutagenesis and similar methods.
			P9, line 1-7 General comment: The document is supposedly focusing on synthetic biology, but throughout the text genetic modification and genetic engineering is interchangeably used to mean synthetic biology. This technical error should be corrected throughout the document.	The SCs consistently use "SynBio" as a further development in biotechnology, which further extends genetic modification through genetic engineering. This is in line with our definition.

			P9, line 1-2 "Research approaches to streamline and standardise the methods for submitting genetic modification data and genetic parts information to risk assessors across EU Member States." Comment: this statement is made repeatedly throughout the text, however it remains unclear whether this proposal is addressing data that is generated during contained use, or is intended for data from organisms that are intended for industrial applications or environmental release. Suggested edit: please clarify the scope of the intended data collection.	The SCs do not advocate the restriction of this kind of standardized data collection to a specific type of application. In view of the speed of development of SynBio, this should apply to both contained use and environmental applications.
			P9, line 10-12 The research priority described here for minimal cells is desirable for any modified organism, and is not specific to organisms developed through synthetic biology.	We agree with this comment and have emphasised this research priority under the heading "General recommendation".
			P9, line 5-7 Also page 31, lines 40-45; page 38, lines 15-20; page 39, line 8-13. We support the use of GMOs with a history of safe use as comparators.	Thank you. No edits required.
			P9, line 13-15 Environmental safety assessments for minimal cells should be conducted on a case-by-case basis and would not merit evolutionary fundamental research. Minimal cells with increased genetic robustness focused on producing a specific product in high amounts will less readily survive in the environment as they will be optimized to grow in specific media, usually not the typical natural substrate. They would produce less secondary metabolites that are non-essential in single-species cultures in defined media. In other cases, increased genetic robustness might inherently equip the microorganism to more effectively process and grow on its natural substrate or be more competitive versus other microbes, and in that case the above-mentioned biosafety design research priority would be desirable e.g., to design other biocontrols that would limit environmental robustness.	The SCs disagree with this view. Characterization of "organisms with respect to evolutionary fitness, ecological competitiveness, degree of horizontal gene flow, susceptibility to viruses, diseases and predation" goes beyond what is routinely necessary within the existing GMO risk assessment. Here, more fundamental data acquisition is required, beyond individual GM organisms.
			P9, line 28-30 Recommendation to "establish a framework" to characterise xenobiologic organisms. This is not necessary as there is no gap – existing GMO risk assessment frameworks apply.	The SCs disagree with this comment. Please see the previous response.

13	EuropaBio, d.carron@europabio.org, Belgium	EXECUTIVE SUMMARY	P9-10, line 39-42; 1-10 Additional research recommendations Comment for the entire paragraph: the text reads as if all SynBio organisms are a risk for the environment by default, and lacks the recognition that some may not have the potential to cause harm. The issues listed are relevant, however, a case-by-case assessment will be needed to identify specific threats.	The SCs would not like to reduce the scope of these recommendations, because it is not always possible to establish risk at an early stage. The SCs aimed for a precautionary approach.
			Suggested edits: p10, lines 1-3: add text (in bold) to existing sentence "Impacts from accidental or intentional introduction of SynBio organisms that have the potential to cause harm into the environment with emphasis on the effect on habitats, food webs and biodiversity" p10, line 4: add text (in bold) to existing sentence "Vertical and horizontal gene flow when this phenomenon may result in negative impacts on the environment."	The SCs do not agree with this edit. However, a clarifying sentence was added: "Prioritization of impact assessments can be based on prior knowledge available". The SCs would not like to reduce the scope of these recommendations, because it is not always possible to establish risk at an early stage. The SCs aimed for a precautionary approach
			p10, line 6: "de extinction " and the debate around it" Delete, as this is not falling with the timeframe stated by the SCs (2020) p10, lines 9-10: add text (in bold) to existing sentence "The environmental performance of SynBio processes and products, considering the full product life cycle and taking into account established processes which SynBio might be replacing"	The debate around de-extinction is on-going and therefore, it is relevant and thus, reflected in the Opinion.
14	EuropaBio, d.carron@europabio.org, Belgium	EXECUTIVE SUMMARY	1. Background P11, line 17: Add text (in bold) to existing sentence "In addition to the benefits of SynBio…." edit to "in addition to the expected benefits of SynBio…"	The SCs agree with this comment and changed "benefits" to "promised benefits".
			P11, line 19-21 Add text (in bold) to existing sentence "A precautionary approach in accordance with ….products generated by SynBio" edit to: "A precautionary approach in accordance with ….products generated by SynBio when such organisms, components and products are likely to cause harm to human health and the environment"	The SCs considered this edit a restriction of the scope of the recommendations and thus, considered it best not to change the current text.

			2. Terms of Reference P12-15 Sources of information: publications of NGOs that are campaigning against synthetic biology are cited – ETC 2010, FOE 2010, FOE 2012. Other ETC publications are cited but not included in the reference list – ETC 2013 (page 14) and ETC 2013a (page 15). The description of the sources of information described on page 12 (lines 3-10) does not transparently indicate that this type of material would be included.	These publications were considered valid sources and thus cited. These citations were added to the reference list. The SCs edited the description of sources.
15	Paton Michael, Health & Safety Executive, michael.paton@hse.gsi.gov.uk, United Kingdom	EXECUTIVE SUMMARY	Executive Summary Page 7, Line 36 It would be helpful if this were considered in the context of whether these risks are different from those posed by existing techniques of modern biotechnology and if so, to what extent? This would inform the urgency and proportionality to address any identified gaps.	The risks described in the Opinion are discussed in relation to existing techniques as much as possible. Therefore, we have not altered the text.
			Page 7, Line 45 This conclusion seems overly simplistic. The increased numbers could equally apply to extending to non-biological disciplines (eg chemists, engineers). This conclusion seems contrary to the cited surveys (Grushkin 2013, Seyfried 2014) and overall conclusion in the report (pg 26, line 20 "the overall additional risk would be minimal"). This is particularly pertinent given the reviews of citizen science point to activities unlikely to cause harm.	We agree with this comment, but it does not affect the Opinion. Non-biological disciplines are out of scope here and there is no contradiction between this sentence and the conclusion on page 26. "probability of unintentional harm might increase" does not contradict "the overall additional risk would be minimal"
			Page 9, Line 46 This conclusion is sensible but may need to be more innovative in identifying the most appropriate use of materials or approaches to be effective or appropriate for this group of users (eg self-assessment tools, Massive Open On-line Course, "Apps")	There is no line 46 on this page. The SCs assume that line 36 was meant. However, it is not clear how these tools the will help increase and maintain the compliance of citizen science. Therefore, no changes were made in the text.

16	Elbing Kerstin, German Life Science Association (VBIO e. V.), elbing@vbio.de, Germany	EXECUTIVE SUMMARY	General remarks „Genetic part libraries and methods", „Minimal cells and designer chassis", „Protocells and artificial cells", „Xenobiology", „DNA synthesis and genome editing" and „Citizen science" have already been defined as key application areas of SynBio in previous opinions I and II. Besides reasons of consistency there is no rationale why these areas have been identified as particularly relevant to the objectives of the CBD. For matters of consistency we would have had expected to see the six novel SynBio developments as bullet points in all chapters of the opinion, which, however, is not the case. For example, there is no pronounced statement on "DNA synthesis and genome editing" in the Opinion or in the corresponding executive summary although a lack of knowledge is mentioned on pages 30 and 44ff. Suggested edit: Adjust the structure of the opinion. Social, governance, ethical, and security implications of SynBio are explicitly outside the scope of preliminary opinion III. However, within the text several references to these issues can be found. Suggested edit: Delete these passages throughout to arrive at a more concise opinion that focuses on the original scope. As terms are not consistently used throughout the text we suggest proper copyediting. In particular, the terms "genetic modification" and "genetic engineering" seem to be used synonymously to mean synthetic biology.	The points raised have been addressed in response to other comments. No further edits are necessary. This is intentional because the recommendations were addressed under "genetic parts" and "minimal cells and designer chassis". This is now clarified in the Opinion. We agree that the analysis of research priorities takes place in a broader context, including social, governance, ethical, and security implications. The text was edited. The SCs consistently use "SynBio" as a further development in biotechnology, which further extends genetic modification through genetic engineering. This is in line with our definition.

			P7, line 30-33 Yet, SynBio does not produce "varieties of organisms, including de-extincted species" Especially research on de-extinction is speculative and clearly beyond the timeframe of opinion III (2020). Suggested edit: "Beyond 2020, SynBio may lead to products or organisms, which could destabilise conservation efforts and diminish support for conservation due to reduced focus on species and habitat preservation".	It is noted that the timeframe of the Opinion is 10 years from now. A main point here is that there is an on-going discussion about the prospect of de-extinction in the long-term future, which might have a negative impact on current conservation efforts. The text was adapted to make this clear.
			P8, line 4-6 New approaches are only needed if it is likely, that the organism, process or product developed with SynBio might cause harm. Suggested edit: "New approaches such as new forms of biocontainment and new biocontainment strategies to manage environmental and health risks will be necessary where such risks are identified for a particular SynBio product."	The suggested edit does not take into account any precautionary containment. This is expressed with the current wording.
			P8, line 26-29 Chemical and radiation mutagenesis, besides others, are well established methods for genetic modifications that result in large, simultaneous and pervasive changes in the genome of the treated organism. Thus, the statement „The use of genome editing methods allows (…) a more pervasive change to the genomes of living organisms than those obtained by traditional genetic modification techniques" is incorrect. Suggested edit: "The use of genome editing methods in a multiplexed fashion allows the simultaneous generation of a large number of variants, the genome-wide modification of organisms and a pervasive change to the genomes of living organisms comparable to the products of already established mutagenesis techniques with safe use." Delete sentence "This might create additional challenges for risk assessment".	Chemical and radiation mutagenesis are not considered targeted methods and as such do not lead to intentional pervasive changes as in SynBio.
			P9, line 1-2 The idea of streamlining and standardising across EU member states the methods for submitting genetic modification data and genetic parts information to risk assessors has been mentioned in Opinion II already. VBIO supports the idea of transparency. However, it has to be considered that a forced complete disclosure might discourage scientists to submit confidential business information to the risk assessors. In this context, the scope of the data collection (industrial applications or environmental releases) should be defined more precisely.	The SCs do not advocate the restriction of this kind of standardized data collection to a specific type of application. In view of the speed of development of SynBio, this should apply to both contained use and environmental applications.

			P9, line 28-30 To characterise xenobiologic organisms the existing GMO risk assessment frameworks can be used. So far there is no necessity to establish a new framework.	The SCs agree the word "framework" is not specific enough and have clarified it by using "methodology" instead of "framework".
17	Fears Robin, EASAC, robin.fears@easac.eu, United Kingdom	3. SCIENTIFIC RATIONALE	The Opinion notes the outputs of discussion within the Convention on Biological Diversity (section 3.1.2). The exploration of the global relevance of the potential environmental implications of synthetic biology research and innovation requires the European Commission also to take more account of what is happening outside of the EU in terms of the debate about appropriate regulatory frameworks and the likely impact of the advancing science. In our response to part 2 of the consultation, EASAC referred to the work of IAP, http://www.interacademies.net/10878/Scientific_Opportunities_and_Good_Governance.aspx, in commenting on some of the environmental issues raised by SBSTTA of the Convention on Biological Diversity, prior to the Conference of the Parties in 2014. In addition to the helpful comments made in the draft Opinion, it would now be useful for the European Commission to take into account other developments internationally. For example: (i) In the USA, the OSTP initiative to update the coordinated framework across Federal Agencies for the Regulation of Biotechnology (https://www.whitehouse.gov/blog/2015/07/02/improving-transparency-and-ensuring-continued-safety-biotechnology), and assessment of risks associated with future products, which also requires coordinating support for the science that informs regulatory activities. The particular relevance of this OSTP initiative to synthetic biology was highlighted by http://www.synbioproject.org. (ii) Globally, the OECD 2014 report "Emerging policy issues in synthetic biology" emphasised the importance of international standardisation in risk assessment approaches and regulation. It will be valuable if the Opinion could discuss how best the European Commission can engage in international discussion and joint work with other advisory groups and other policy-makers.	This information is appreciated, but the request goes beyond the mandate questions for the SCs.
18	EuropaBio, d.carron@europabio.org, Belgium	3.1. To review the state of the scientific knowledge concerning specific	P14, line 19-20 The UNEP/CBD/COP/12/INF/11 is not qualifying as scientific literature and therefore, it is recommended that the description of the reference sources takes this into account. Suggested edit: delete the word	The SCs clarified this with the following edit: "'These include potential positive and negative impacts as highlighted in UNEP/CBD/COP/12/INF/11"

		risks to the environment and synthesise it	"scientific" in line 20.	
			P14, line 39-40 Also page 35, lines 15-17. The comments needs to be placed in context – e.g. how does the extraction of biomass from agricultural land for bioenergy applications compare to other forms of agriculture with regard to impact on soil fertility. In addition, this is not specific for synthetic biology., this could happen with all biomass utilization technologies including just burning it.	We agree that the extraction of biomass from agricultural land for bioenergy applications is not per se necessarily different from other forms of agriculture with regard to impact on soil fertility. The issue refers to the fact that additional intensification of agriculture with a new end product, may lead to effects on soil fertility and to overcome this, additional nutrients may be used. We agree that this issue is not specific to Synthetic Biology but new possible directions in this area, facilitated by the use of Synthetic Biology, may lead into further worsening of this issue.
			P14, line 40 The article by Fixen (2007) is not quoted in the correct context, please update the context focusing on nutrient management or delete reference.	This sentence was edited to reflect the meaning: "SynBio bioenergy applications could lead to increased extraction of biomass from agricultural land, which may decrease soil fertility and would potentially affect nutrient use and management (ICSWGSB 2011; Fixen 2007)."
			P14, line 41-43; 44-45 These two points concern socio-economic considerations, which are not within the scope of this opinion. Further, the references for this information are NGO publications and not scientific literature as referred to in lines 19-20 as being the basis of the section. Suggested edit: delete these two points.	This section deals with "key issues in Decision XI/II of the CBD that affect SynBio. The SCs consider these points valid for this discussion and therefore included them. NGO publications should be included in this debate if they are considered of strong enough scientific quality to qualify for inclusion.

			P15, line 13-29 Suggested edit: the first two points of this section should be deleted or revised to reduce length and more accurately indicate that SynBio application in this area is speculative and beyond the 2020 timeframe of the Opinion. In particular, the sentence on lines 25-27 should be deleted as it is unnecessarily provocative.	This sentence is a direct quotation from a key scientific publication and therefore, it is not possible to edit it.
			P15, line 34-35 Refers to genetically modified crops; there needs to be a further statement such as "GM crops created with the aid of SynBio approaches may provide similar benefits".	The SCs consider this statement too general and therefore did not edit the text in the Opinion.
			P15, line 42-43 Source not included in the reference list. This statement should be substantiated with a realistic example and the ETC reference should be removed as the section is supposed to be based on scientific literature (see page 14, lines 19-20).	The reference is added to the Reference List. The SCs consider that there is no need to add further examples, because they would not add any further clarification. We consider that NGO publications should be included in this debate if they are of high enough scientific quality.
			P16, line 7-9 Suggest changing the language to: "It may be possible that SynBio alternatives for chemical products will not prove more sustainable than current production practices. This scenario was argued for the production of bioplastics in Schmidt (2012)." The ETC reference should be removed as the section is supposed to be based on scientific literature (see page 14, lines 19-20).	The SCs do not see the need to change the wording. The difference between the suggested edit and the current text seems marginal and does not offer further clarification.
19	EuropaBio, d.carron@europabio.org, Belgium	3.1. To review the state of the scientific knowledge concerning specific risks to the environment and synthesise it	P17-23 Aichi targets General comment: Table 1 should be removed from the Opinion. It is not clear why the Aichi targets are incorporated into the Opinion, since their scope extends well beyond that of the three questions that the SCs are mandated to address, and the comments provided by the SCs in the table add nothing to the Opinion in the remainder of the document. The Opinion states that 'social, governance, ethical and security' implications of SynBio are outside of the current mandate (page 7, lines 16-18). In Table 1, the SCs make comments that concern socio-economics (targets 14 and 18). The language in the table is general, and the comments are predictions or speculative. The comments should be substantiated with examples from the scientific literature. Otherwise the language should be tempered so that it is neutral and not overstating predicted impacts.	Table 1 provides an important contribution to identifying and contextualizing the potential risks and impacts of SynBio on the environment and biodiversity. Therefore, no edits were done.

			Suggested edit: Given that much of the table is empty (i.e. "none" entries), and that for several targets (no. 4, 7, 8, 9, 14, 15) the comment made against "genetic parts" applies generally to SynBio, the table should be greatly reduced or completely removed, with a general discussion about the Aichi targets in the text. Suggested rewrites are provided below for some of the targets which could be incorporated into a general discussion. There also needs to be an explanation of why these targets have been addressed as this in not provided in the Opinion (e.g. see p16 lines 27-32). P17, Aichi target 1 Suggest the following rewrite of the comment in 'genetic parts': 'Synbio could promote a greater awareness of the value of biodiversity as a source of, and inspiration for, genetic parts.' Suggest the following rewrite of the comment in 'xenobiology': 'The ability to create new organisms could have the effect of reducing the perceived value and need to conserve biodiversity, based on [insert example] .' P 18, Aichi Target 4 The comment in 'genetic parts' applies generally to SB and should be in a separate column for such comments. Suggest the following rewrite (as a general comment): 'Production methods based on SynBio could reduce consumption of non-renewable resources (e.g. oil), and allow for more sustainable production of i.a. fuel,chemicals or pharmaceuticals. These methods may require production of raw materials (e.g. sugar) which could have a detrimental impact on biodiversity if unsustainable practices are used.' P18, Aichi Target 5 Content is missing. P19, Aichi Target 7 The comment in 'genetic parts' applies generally to SB and should be in a separate column for such comments. Suggest the following rewrite (as a general comment): 'Genetically modified crops produced by using SynBio approaches could allow for even more sustainable production practices, e.g. increased tolerance to heat, drought, and other environmental stress, improved quality and content of animal feed, food and energy sources, reduced use of pesticides and herbicides have been quantified with some established GM crops (e.g. Bt crops). Such practices could have a detrimental impact on biodiversity if they are not managed taking into account the potential impacts on the environment.' P19, Aichi Target 8 The comment in 'genetic parts' applies generally to SB and should be in a separate column for such comments. P19, Aichi Target 9 The comment in 'genetic parts' applies	

			generally to SB and should be in a separate column for such comments. P20, Aichi Target 10 Typos – '2015!'	
20	EuropaBio, d.carron@europabio.org, Belgium	3.1. To review the state of the scientific knowledge concerning specific risks to the environment and synthesise it	P21, Aichi Target 13 Suggest the following rewrite of the comment in 'genetic parts': 'Synbio could promote a renewed appreciation of the value of genetic diversity as a source of genetic parts, which could assist with developing and implementing strategies to safeguard genetic diversity'. Suggest the following rewrite of the comment in 'DNA synthesis': 'DNA synthesis may allow the re-synthesis of genomes, which could potentially reduce the incentive to maintain landraces and wild relatives'. P21, Aichi Target 14 The comments are outside the scope of the Opinion and are socio-economic in nature. The claim that SynBio design goals pay "…very little attention…to the interest of marginalised communities, and the poor and vulnerable." is factually wrong and needs to be corrected. The comment in 'genetic parts' applies generally to SB and should be in a separate column for such comments. Suggest the following rewrite of the comment in 'genetic parts'(as a general comment): 'SynBio has the potential to provide tools that improve the quality of life of indigenous and local communities, and the poor and vulnerable, e.g. biosensors for testing water quality [insert reference].' P21 Suggest that the comment for 'citizen science' is rewritten: 'Citizen science has helped to empower women, indigenous and local communities and the poor and vulnerable, e.g. [insert example].' P22, Reference to the Nagoya Protocol. Delete "So, DNA sequencing and synthesis could provide a loophole to the Nagoya protocol". We strongly believe that it is beyond the remit and mandate of the scientific committees to provide opinions on the Nagoya protocol. P22, Aichi Target 15 The comment in 'genetic parts' applies generally to synthetic biology and should be in a separate column for such comments. Suggest the following rewrite of the comment in 'genetic parts' (as a general comment): 'Organisms could be created by SynBio approaches that have traits that confer tolerance to abiotic stresses (e.g. drought, salinity) that allow restoration of	Table 1 provides an important contribution to identifying and contextualizing the potential risks and impacts of SynBio on the environment and biodiversity. Therefore, no edits were done.

			degraded agro-ecosystems. ` P22, Aichi Target 16 The comment for 'DNA synthesis' refers to a 'loophole'. This is a provocative and speculative comment, especially since the Opinion III does not examine legal aspects of the Nagoya protocol and its country application. This is not within the scope of the questions being addressed in the Opinion. Suggest that this comment is removed. p23, Aichi Target 18 This target and comments are well outside the scope of the Opinion and the comments should be removed.	
21	McGrath Peter, IAP - the global network of science academies, mcgrath@twas.org, Italy	3.1.3. Potential impacts of SynBio applications on conservation and sustainable use of biodiversity	The following comments all refer to Table 1 (pages 17-23 - line nos not specified in document). Goal A, Aichi target 1, Xenobiology: Disagree - The term 'artificial biodiversity' may trigger public tension and is thus unnecessary, especially as we did not see the term emerge during the GMO debate. Goal A, Aichi target 1, DNA synthesis: Genome editing may produce limnited number of variants for certain applications, but not 'diversity' per se. Goal B, Aichi target 4, Genetic parts: Disagree - A large bioprocessing industry has existed for many years. SynBio will complement this and have effects in some areas, but no more so than the traditional bioprocessing industry. Goal C, Aichi target 13, Genetic parts: Colleagues from the Chinese Academy of Sciences have raised a doubt over whether the negative impact is valid. There wil lstill be a need to conserve landraces and wild rlatives, etc. Goal C, Aichi target 13, DNA synthesis: Again, colleagues from the Chinese Academy of Sciences doubt that this will be an issue. Goal D, Aichi target 14, Genetic parts: We agree with this synopsis and this is perhaps an area that targeted EU funding may address in the coming years.	The SCs don't foresee "public tension" as the result of this word choice; the fact that the term did not emerge during the GMO debate just indicates that SynBio is rapidly moving beyond what was considered possible in the GMO field just a few years ago. The statements made here are considered personal views, which do not provide new evidence and therefore do not require any change in the current text.

22	Scott Deborah, Engineering Life project, University of Edinburgh, Deborah.Scott@ed.ac.uk, United Kingdom	3.1.3. Potential impacts of SynBio applications on conservation and sustainable use of biodiversity	section 3.1.3 – pages 14-16 As I understand the EC's mandate to the Scientific Committees, this question was intended to feed into the CBD's engagement on synthetic biology, most likely by providing "relevant information on components, organisms and products resulting from synthetic biology techniques that may have impacts on the conservation and sustainable use of biological diversity and associated social, economic and cultural considerations" as requested in Decision XI/11 para 3a. With a few exceptions (the discussion of Saygin et al (2014) on bio-based materials and some citations for biofuels), this section summarizes the CBD document on potential impacts. This does not seem to materially assist the CBD's work. More importantly, the CBD document was not restricted to "the foreseeable future," and therefore engaged with promissory language from scientific biologists and concerns responding to those promises. By my understanding, de-extinction projects are unlikely to restore ecological richness in the next 10 years, although the promise of de-extinction may destabilize approaches to conservation in that time frame. Providing new / unexamined literature in these areas would be helpful for CBD processes. Providing a summary of the CBD's existing document, without including its overall framing, does not seem helpful.	The mandate required the SCs to review the state of the scientific knowledge concerning specific risks to the environment. The SCs considered the CBD-documents valuable input before answering this question in section 3.1.4.
			section 3.1.3 – pages 17-23 (Table 1) General Comments I can see the potential value in systematically considering the interplay between the Aichi Targets and synthetic biology, but this Table is not, at this point, a helpful resource. It seems rather ad hoc and, again, not based on a systematic consideration of synthetic biology in the foreseeable future. Such a table could be a very helpful resource for CBD processes, the treaty Parties, and interested researchers and laboratories if it systematically identified research gaps,	See the SCs response to comment 19.

			relevant uncertainties, outstanding concerns, and potential goals for synthetic biology, ecologists, social scientists, and others. Throughout the table, the category of "citizen science" seems to not be restricted to synthetic biology engagement. This seems overly broad. I think it's only helpful to consider the role of citizen scientists engaged with synthetic biology, in which case I don't see how they can, for example, help to increase awareness of traditional knowledge (p23, Target 18).	
			p17 Table 1 Target 1 – Aichi Target 1 relates to the public's awareness of the values of biodiversity. The genetic parts point is related to sustainable use (targets under Strategic Goal B).	The SCs argue that the use of genetic parts increases the awareness of the values of biodiversity.
			p19 Table 1 Target 8 - Is the projected timetable such that polluting industrial processes could be replaced by synthetic biology-enabled processes by 2020? Is it anticipated that genetically modified micro-organisms for cleaning up pollutants won't be ready for field or environmental release by 2020?	The SCs acknowledge that this is difficult to predict.
			p23 Table 1 Target 19 – This target is not just about improving knowledge, but also about the sharing, transferring, and application of knowledge. It is thus an appropriate Target for considering intellectual property in the context of synthetic biology.	The SCs agree and have merged this with the original text.
23	Sanders Dale, John Innes Centre, Dale.Sanders@jic.ac.uk, United Kingdom	3.1.3. Potential impacts of SynBio applications on conservation and sustainable use of biodiversity	We consider that gene synthesis and gene editing should not be grouped as a single heading, but rather gene synthesis should be considered along with 'parts'. There is a definite risk of synthesising parts that have dangerous function either intentionally or unintentionally as part of random approaches. This would also make more sense with regards to discussion of the Nagoya protocol on access to genetic resources on P16 Line 29 and Table D on page 22. P21, Strategic Goal D, Aichi Target 14. Despite being a young field, significant examples are already beginning to emerge that demonstrate the impact and value of synthetic biology for public benefit, such as large-scale, cost-effective and sustainable production of pharmaceuticals in microbes (e.g.	Thank you for sharing your views. No edits were done.

			the anti-malarial artemisinin; Paddon and Keasling, 2014) and rapid vaccine production to control epidemics using plant-based gene expression technology (e.g. the HyperTrans system; Sainsbury and Lomonossoff, 2014). There are also large international research programmes (e.g. the Gates-funded ENSA, C4-rice, and RIPE programmes) as well as small proof of principle projects (e.g. iGEM projects) that are aimed specifically at using synthetic biology to solve problems in developing countries, for marginalised communities, the poor and vulnerable. The iGEM competition actively promotes the involvement of teams from developing countries. Science is expensive for developing countries and that is unlikely to change in the near future. However, the drive in synthetic biology to simplify the design process, create cheaper, more efficient and open methodologies and tools, and promote sharing of e.g. DNA parts are contributing to the accessibility of this field to a wider range of users, as seen in the level of engagement from citizen science groups. In addition, exchange programmes that mobilise scientists between developed and developing countries (e.g. the JIC-BecA- ILRI hub alliance and Science for Africa) support research projects that seek to solve problems specific to developing regions.	
24	Paton Michael, Health & Safety Executive, michael.paton@hse.gsi.gov.uk, United Kingdom	3.1.3. Potential impacts of SynBio applications on conservation and sustainable use of biodiversity	Page 15, Line 10 The emerging technology of gene drive is not considered in the Opinion under genome editing – is this because the Opinion does not consider it to be a SynBio technique? Although current risk assessment methodologies focus on minimising gene transfer and impact on non-target species, gene drive is intended to promulgate genetic changes through target species to either suppress or alter populations in the environment, (in some cases to remove their capacity to transmit diseases). The potential benefits in term of disease eradication are apparent however the environmental impact is less clear.	The SCs indeed do not consider "gene drives" as falling under the definition of SynBio, as "the application of science, technology and engineering to facilitate and accelerate the design, manufacture and/or modification of genetic materials in living organisms". The methods used are related, but "gene drives" aim at modifying the genetic composition of populations, not of individual organisms; a full analysis of the risks and implications of "gene drives" would be outside the scope of this Opinion. We have, however, clarified in the text that this technology needs further analysis.

25	Elbing Kerstin, German Life Science Association (VBIO e. V.), elbing@vbio.de, Germany	3.1.3. Potential impacts of SynBio applications on conservation and sustainable use of biodiversity	General remarks This chapter gives a concise overview about the possible impact of SynBio with relevance to certain applications. Nevertheless we would have preferred a more elaborated presentation of direct and indirect effects as well as of accidental and planned effects. For example, the negative impact of an accidental release of organisms is only mentioned for bioenergy applications (page 14, 46-47), but not for the other applications.	Direct and indirect effects are addressed in the Opinion.
			P14, line 21 ff We like to mention, that a number of consequences depicted for SynBio applications to bioenergy (like biomass extraction or loss of biodiversity) are a matter of land use and producing systems and thus is not exclusive to SynBio products.	The SCs agree with this comment. However, if SynBio tools are used to unlock the biofuel potential from too expensive to economically justifiable, then this will have an impact on land use. SynBio does influence it.
			P15, line 13-29 Wildlife-targeted applications of SynBio aiming at the restoration of extinct species are far beyond the time frame of this opinion (2020). They should be mentioned as future issues only.	The SCs agree with this statement. The time frame of the Opinion is 2025, and therefore, cannot be ruled out, but should not be emphasised either as expressed by the careful wording
			P 17-23 (Table 1) Development of SynBio might interfere with Aichi targets. But it is doubtful whether the Aichi targets (2020) are the right framework to judge possible long-term impacts of SynBio on biodiversity. In addition, Aichi targets include socioeconomic issues, which are outside the scope of this opinion making it difficult to align them to the six key areas of SynBio. A number of comments are not biunique to one of the six areas or are general to SynBio. Please note, that within the systematics of Aichi targets no accidental impact of SynBio organisms can be mapped, which biases the overall evaluation. The general content of table 1 does not deliver a compulsory assessment but is more anecdotic. The bullet points are general and in a substantial number of cases not exclusive for SynBio. Often the comments are speculative and not based on references to scientific literature. We suggest to revise table 1 as follows: Aichi target 5 No content? Aichi target 7 Reduction of pesticides through genetically modified organisms (SynBio products?) is only one element of sustainable management. Thus, the statement for „genetic parts" is only anecdotic and may be misleading.	Aichi is the UN consensus of what to do to safeguard biodiversity. In the view of the SCs this cannot be considered as doubtful

			Aichi target 8 The statement "Industrial processes that produce a lot of pollution could be superseded by more environmentally friendly biological replacements" is much too general. The specific relevance of SynBio is not clear.	The SCs agree and have edited this as follows: …"could be superseded by more synthetic biology based environmentally friendly replacements."
			Aichi target 14 Spreading of general biological knowledge on biodiversity and sustainable management definitely contributes to the empowerment of women, indigenous and local communities, poor and vulnerable groups - But there are no references in literature, which confirm this with respect to specific knowledge of synthetic biology.	Re literature reference, when having to speculate about the next 10 years then it is likely that there are no citations available. We ware asked to foresee possible impacts, which we have done based on our common knowledge in this area.
			Aichi target 16 DNA sequencing and synthesis could provide a loophole to the Nagoya Protocol and its implementation regulations. This is due to weaknesses of the Nagoya Protocol and its implementation rather than a risk specifically arising from SynBio techniques. Although legal aspects are not the primary scope of this preliminary opinion, we claim, that this issue has to be monitored carefully. Solutions have to be found which do not hamper basic research.	We can confirm this.
			Aichi Target 18 The comments should be removed because this target addresses questions outside the scope of preliminary Opinion III	Table 1 provides an important contribution to identifying and contextualizing the potential risks and impacts of SynBio on the environment and biodiversity. Therefore, no edits were done.
			Aichi target 19 There is no specific attribution of the statement "None, possibly positive…" to any of the head of columns. Does this mean that this statement is true for each of them?	Yes
26	Fears Robin, EASAC, robin.fears@easac.eu, United Kingdom	3.1.4. Specific risks to the environment per research area	A lot of detail is presented in the comprehensive Opinion about hypothetical risks but it is difficult to assess relative probabilities and in many cases the synthetic biology methodology is at too early a stage for evaluation of additional options for risk assessment. It is important not to over-emphasise hypothetical dangers. Rather than commenting on this wide range of potential concerns in detail at this stage, EASAC suggests that there is a more pressing strategic issue – how to confer regulatory authorities and policy-makers with the receptivity to evaluate the new opportunities that will come within range in consequence of the advances in science and technology. The scientific community has a responsibility to educate	These remarks are appreciated, but the request goes beyond the mandate questions of the Commission to the SCs. There seems to be a conflation between risk assessment, risk analysis and risk management. SCs task was to explore potential safety challenges and gaps in risk assessment, not to provide a list of potential benefits. In risk management the benefits need to be considered, as well as the risks. The SCs provides info on risks.

			regulators about emerging technologies so that they can exercise their regulatory roles in an informed, consistent and coherent way (see also the discussion at the New York meeting April 2015 "Engineering biology for science and industry: accelerating progress", http://nancyjkelley.com/wp-content/uploads/Meeting-Summary.Final_.6.9.15-formatted.pdf). There is other guidance that is relevant to the broader regulatory framework, which has appeared since publication of parts 1 and 2 of the Opinion. For example, the report from the World Economic Forum (2015, "Part 2 Risks in focus: 2.4 Engineering the future: how can the risks and rewards of emerging technologies be balanced?", http://reports.weforum.org/global-risks-2015) addresses the issues of (i) where to regulate (national or international level, and if national/regional how to produce global coherence; (ii) timing of regulation of technologies with an uncertain future path; and (iii) who regulates – allocating responsibility across existing regulatory bodies. There are common principles underlying the risk assessment and regulation of synthetic biology and other emerging technologies.	
27	Scott Deborah, Engineering Life project, University of Edinburgh, Deborah.Scott@ed.ac.uk, United Kingdom	3.1.4. Specific risks to the environment per research area	p26 DNA synthesis and genome editing – As the increased speed of modifications is noted, it also seems relevant to note that new genome editing techniques may pose challenges to risk assessment by falling outside of many current risk assessment frameworks for genetic engineering.	The SCs aimed at pointing to the use of technologies for DNA synthesis and genome editing involving TALEN, CRISPR and other engineered nucleases but also to the approach known as Multiplex automated genome engineering (= MAGE). This is clarified in the Opinion and references were added. '
28	Sanders Dale, John Innes Centre, Dale.Sanders@jic.ac.uk, United Kingdom	3.1.4. Specific risks to the environment per research area	Our view is that potential risks from synthetic biology work are highly variable. At one level research will involve high precision, targeted and well understood changes usually of extremely low risk whereas at the other extreme work will be of a complex nature with more uncertainty surrounding the level of risk. In none of the three Opinions is there a mention of gene drives made using gene editing technologies. This needs be addressed. The inventors of these technologies have themselves acknowledge associated risks and the necessity for regulation (Oye et al., 2014; Akbari et al., 2015).	The SCs indeed do not consider "gene drives" as falling under the definition of SynBio, as "the application of science, technology and engineering to facilitate and accelerate the design, manufacture and/or modification of genetic materials in living organisms". The methods used are related, but "gene drives" aim at modifying the genetic composition of populations, not of individual organisms; a full analysis of the risks and implications of "gene drives" would be outside the scope of this Opinion.

				We have, however, clarified in the text that this technology needs further analysis.
29	EuropaBio, d.carron@europabio.org, Belgium	3.1.4. Specific risks to the environment per research area	The document seems to imply generically, in several places, that additional layers of containment are needed for all uses of SynBio. In our view a perspective with greater degrees of differentiation is needed. Indeed, for contained-use applications, e.g., only those using synthetic DNA constructs to generate "self-cloned" organisms with decreased fitness in the environment, such additional layers of containment would seem to us to be unnecessary. For xenobiology, on the other hand, the picture may be different.	The SCs emphasise that the currently available methods for containment will be insufficient for the types of applications envisaged in the near future. To avoid a bottleneck in the regulatory approval process, novel biocontainment strategies should be developed and characterised. The SCs agree that that may not necessarily be applied to all products, but should be chosen carefully. Opinion III recommends increasing the number of containment options.
			P24, line 3-5 It is appreciated that the SCs acknowledge the probabilistic nature of the generic risks and that more in-depth assessment is needed for each individual point for its relevance.	Thank you for your comment. No edits required.
			P24, line 6-7 The first "generic" risk mentioned is: "Accidental release of SynBio organisms engineered for contained use may lead to their survival and propagation in the environment." This is, in our opinion, the least likely and least relevant risk; if engineered specifically for contained use (where the target typically is to produce substances at high yield, thereby decreasing availability of cellular resources for other processes such as survival), they are perforce in the vast majority of cases less fit in the environment compared to their progenitors.	The order of the generic risk is not in order of priority. This is clarified in the introductory text to these bullet points.
			P24, line 9-15 In the section where "Accidental release could affect water/wastewater treatment processes (specifically biological processes) through the interaction with indigenous microorganisms (Unnithan et al., 2014; Guo et al., 2014) as well as they may be undertaken to unpredictable genetic changes/transformations (e.g., mutants formation, antibiotic resistance transfer) in chemical oxidation/disinfection (e.g., Cl2, ClO2, O3, UV-C radiation, advanced oxidation processes etc.) based water/wastewater treatment plants." we are	The SCs agree with this comment and have removed some detailed information. The accidental release is applicable to both deliberateg and contained use.

			unsure why this point is addressed in far greater detail than other sections. In addition, it is unclear to us why this should be a specific risk of contained use ("accidental release") but not for deliberate release.	
			P24, line 22-23 The scope of the opinion until - 2020 makes this last bullet point irrelevant for the current discussion and it is proposed that the text is deleted.	Aichi targets are 2011-2020, while our time horizon is until 2025.
			P24, line 25 At the contrary, constructs becomes much more well characterized and "deliberate". It is true that a lot of diversity is generated, but it is screened and only one or a few strains are passed on for application testing.	The SCs argue this point as explained in lines 27-34 on page 24.
			P24, line 32-34 The document states here, and in other parts of the text that a challenge to risk assessment might be the lack of appropriate comparator organism. It is important to recognise that RA can be conducted in different ways, and it does not necessarily depend on the presence of comparator organism.	The SCs understand this comment and agree with it, as stated in Opinion II.
			P24, line 27 The constructs are characterized before they are passed on. "emergent" properties cannot be ruled out but these could as well occur in "classical" improved strains (and do so). If the system does what it is supposed to do and do not get additional properties this is not a real risk.	The SCs stated that there may be an increase in the frequency of uncharacterised components or the diversity of biological functions and this necessitates a risk assessment.
30	EuropaBio, d.carron@europabio.org, Belgium	3.1.4. Specific risks to the environment per research area	P26, line 4 Replace "tested for risk to" with "assessed for potential risks to".	A potential risk is redundant because the term risk refers to a probability. Therefore, it is not necessary to use the term potential.
			P26, line 12 The word 'easily' is an exaggeration, delete it or replace with 'theoretically'	The SCs deleted the word easily.
			P26, line 10-14 Also present in p8, lines 26-28 The presumption that DNA synthesis and genome editing accelerate genetic modification and increase the range and number of modifications is not factually correct, because it is at best comparable to other well established methods of mutagenesis. What might be different is the precision and specificity of the method compared to alternative existing ones. Suggested edit to the paragraph: "The new technologies for DNA synthesis and genome editing improve	The SCs aimed at pointing to the use of technologies for DNA synthesis and genome editing involving TALEN, CRISPR and other engineered nucleases but also to the approach known as Multiplex automated genome engineering (= MAGE). This is clarified in the Opinion and references were added.

			the precision and accuracy of genetic modification and increase the range and number of modifications that are theoretically possible." "The increased speed of modifications might pose challenge to risk assessment…" This statement needs to be supported by a realistic example. In what circumstances the risk assessment will be challenged considering that alternative modification methods that have been applied for long time and that result in multiple and very fast changes in the genome (chemical mutagenesis) are not considered to pose a challenge to risk assessors? In several instances, it is stated that "The increased speed of modifications might pose challenges to risk assessment, while not in itself creating new risks" (e.g., page 26, lines 13-14). In our view there is a lack of explanation as to what these "challenges" are. In our view if the focus is on the properties of the final product (where the full emphasis should be), the speed of construction would largely be irrelevant.	
31	Paton Michael, Health & Safety Executive, michael.paton@hse.gsi.gov.uk, United Kingdom	3.1.4. Specific risks to the environment per research area	Page 24, Line 3 When considering the likelihood/probability of accidental releases, it would be helpful to consider the number and type of reported accidents under existing GM regulations. There is requirement to inform the EC of any GM accidents that meet the definition in 2009/41/EC.	The SCs agree with this comment, however, the data are unavailable or unreliable.
32	Elbing Kerstin, German Life Science Association (VBIO e. V.), elbing@vbio.de, Germany	3.1.4. Specific risks to the environment per research area	P24, line 9-15 The risk for antibiotic resistance transfer in waste water plants also apply to natural microorganisms exposed to antibiotics and GMMs. It is not specific to SynBio organisms.	The SCs agree with this comment and thus, this issue was inserted into the "generic" section.
			P24, line 22-23 SynBio activities concerning „de-extinction" will have an impact on biodiversity and ecosystems but this will not be relevant within the time scope of the opinion (2020) Suggested edit: "IN THE LONG RUN: Potential impacts on biodiversity and ecosystems from "de-extinction" (…)	It is noted that the timeframe of the Opinion is 10 years from now. A main point here is that there is an on-going discussion about the prospect of de-extinction in the long-term future, which might have a negative impact on current conservation efforts. The text was adapted to make this clear.
			P24, line 27 As of their nature "emergent" properties cannot be ruled out in advance. But this emergence can also occur in strains modified by any other technique (e. g. chemical or physical mutagenesis).	The SCs agree with this statement. However, this Opinion is on SynBio and does not address chemical or physical mutagenesis.

			P26, line 4 Suggested edit: Replace "New variants must be tested for risk to…" with "New variants must be assessed for potential risks to…"	A potential risk is redundant because the term risk refers to a probability. Therefore, it is not necessary to use the term potential.
			P26, line 8-9 The SCs should specify what is meant by "particular auxotrophies" of xeno-systems.	The SCs agree and changed "their particular auxotrophies" to "their custom-made auxotrophies".
			P26, line 10-14 The claim that DNA synthesis and genome editing accelerate genetic modification and increase the range and number of modifications is not correct. What might be different in comparison to other methods of mutagenesis is the very high precision and specificity. Suggested edit: "The new technologies for DNA synthesis and genome editing improve the precision and accuracy of genetic modification and increase the range and number of modifications that are possible".	The SCs aimed at pointing to the use of technologies for DNA synthesis and genome editing involving TALEN, CRISPR and other engineered nucleases but also to the approach known as Multiplex automated genome engineering (= MAGE). This is clarified in the Opinion and references were added.
33	Cannell Martin, Defra, martin.cannell@defra.gsi.gov.uk, United Kingdom	3.1.5. Prevention of SynBio adverse effects on the environment	Page 26, Line 31: Gressel et al. (2013), for instance, discuss the risk containment of spills of genetically modified microalgae used for biofuels production by physical containment and by genetically precluding the algae from replicating and competing in nature by introducing genes which severely decrease their fitness in natural ecosystems This sentence doesn't read quite correctly. Should it be '…environmental risk' instead of '…risk containment'?	The SCs agree with suggestion of commentator to use "environment risk" or risk instead of containment risk.
34	Scott Deborah, Engineering Life project, University of Edinburgh, Deborah.Scott@ed.ac.uk, United Kingdom	3.1.5. Prevention of SynBio adverse effects on the environment	p26 3.1.5 prevention of adverse effects – Beyond invoking Opinion II, it also seems relevant to discuss here planned (and implemented) projects involving environmental release, such as using genome editing techniques to transform gene drive systems in mosquitoes.	The SCs indeed do not consider "gene drives" as falling under the definition of SynBio, as "the application of science, technology and engineering to facilitate and accelerate the design, manufacture and/or modification of genetic materials in living organisms". The methods used are related, but "gene drives" aim at modifying the genetic composition of populations, not of individual organisms; a full analysis of the risks and implications of "gene drives" would be outside the scope of this Opinion. We have, however, clarified in the text that this technology needs further analysis.

35	Sanders Dale, John Innes Centre, Dale.Sanders@jic.ac.uk, United Kingdom	3.1.5. Prevention of SynBio adverse effects on the environment	A robust and transparent framework is needed to ensure that the risk assessment process and required biosafety controls are appropriate for each case. While safety of new technologies is of course paramount, we do have concerns that synthetic biology activities may potentially be over regulated using the current GMO risk assessment framework, certainly in the case of agriculture-related areas. Synthetic biology is higher precision than traditional genetic engineering, and in many cases we can be confident of the modifications made to an organism and of a low level of risk. We support the committees' opinion that there is a necessity for risk assessments to be reviewed and revised on a regular basis as new information becomes available (which has not happened with GM). Our overall view is that regulatory systems for synthetic biology need to be fit-for-purpose and adaptive in order to enable responsible and safe innovation without over-regulation and the impeding of progress.	Thank you for your support. The SCs agree with the comment "there is a necessity for risk assessments to be reviewed and revised on a regular basis as new information becomes available', but not that SynBio will be "over regulated using the current GMO risk assessment framework".
36	EuropaBio, d.carron@europabio.org, Belgium	3.1.5. Prevention of SynBio adverse effects on the environment	P26, line 35 Typo – replace 'of' with 'or'	The SCs agree with the comment and corrected it in the text.
37	Martin Cannell, Defra, martin.cannell@defra.gsi.gov.uk, United Kingdom	3.1.6. Mitigation of SynBio adverse effects on the environment	Page 27, Line 19-22: Given the difficulties in preventing a biological incident of any type, the main goal of contingency planning should be to mitigate an event whether it is deliberate, accidental, or a naturally occurring release, which may be difficult to distinguish at first. A prepared, efficient international response may limit the size and scope of such releases as well as the implementation of IHR (international health regulations) standards (Gronvall, 2015). This wording suggests that biological incidents are common place, whereas in general containment measures are very successful at preventing biological incidents. Only very serious incidents would require such a response. The suggestion of a co-ordinated international response specific to accidental releases of synbio does not seem proportionate to any risks envisaged for the 10 year time frame, unless it is qualified with examples of the type of incident envisaged by the authors.	The SCs agree that the response should be proportional to the risk and therefore have included the word proportional to the last sentence. In addition the reader is made aware of the requirement for an a priori assessment of the necessity for international notification.

			Page 29, Line 16: Protocells could, in the not so distant future, be further engineered to fully pass the definition threshold of living organisms. In this case, a form of life that is not directly related to any other pre-existing organisms would be generated, which means that no information would be available to evaluate the interaction between newly created and naturally evolved life forms. The capability to produce a protocell that passes the definition of a living organism is indeed a long way distant from reality. By then, future biotechnology regulations will likely have evolved or been amended to allow for such subtle distinctions. An important and highly relevant principle from the GMO regulations, that is unlikely to change, is the 'step by step' principle: "…the introduction of GMOs/SMOs into the environment should be carried out according to the 'step by step' principle. This means that the containment of GMOs is reduced and the scale of release increased gradually, step by step, but only if evaluation of the earlier steps in terms of protection of human health and the environment indicates that the next step can be taken". Thus at least some information is likely to be available to evaluate the interaction between newly created and naturally evolved life forms. It therefore seems incorrect to suggest than no information would be available. Suggested alternative text: In this case, a form of life that is not directly related to any other pre-existing organism could be generated, which means that novel interactions between newly created and naturally evolved life forms are likely to require close assessment	The SCs agree that the aim is that future biotechnology regulations will evolve or will be amended to allow for subtle distinctions. The current text states that no information is available, which is not implied by the suggested edit. Therefore, no edits were done.
38	Scott Deborah, Engineering Life project, University of Edinburgh, Deborah.Scott@ed.ac.uk, United Kingdom	3.1.6. Mitigation of SynBio adverse effects on the environment	p27 3.1.6 Mitigation – lines 19-23 (and Opinion p37 – lines 8-10) – What is meant by a "prepared, efficient international response"? The Gronvall 2015 discussion paper recommends national biosafety norms restricted to laboratory practice,	The SCs agree that this needs further clarification. The response should be proportional to the risk and therefore the SCs have included the word 'proportional' to

			expanded gene synthesis screening, and improved international public health infrastructure. While these are certainly important, there is space for the Scientific Committees to identify other international responses that would more specifically relate to environmental concerns	the last sentence as well as the text 'in specific and high risk cases'. In addition, the reader is made aware of the WHO IHR and its' requirement for an a priori assessment of the necessity for international notification.
39	EuropaBio, d.carron@europabio.org, Belgium	3.1.6. Mitigation of SynBio adverse effects on the environment	P27, line 19-21 Also page 37, line 6. Suggest deleting "given the difficulties in preventing a biological incident of any type'".	The SCs agree with this comment and have edited the text accordingly.
40	Paton Michael, Health & Safety Executive, michael.paton@hse.gsi.gov.uk, United Kingdom	3.1.6. Mitigation of SynBio adverse effects on the environment	Page 27, Line 14 Whilst it is important that such mitigation is in place, this is only relevant where there is a significant risk to the environment. In contained use, the level of containment applied is proportionate to the risk, hence an emergency plan would be appropriate for the highest containment activities but not for activities where there are no or negligible risks.	The SCs agree that the response should be proportional to the risk and therefore have included the word 'proportional' to the last sentence as well as the text 'in specific and high risk cases'. In addition, the reader is made aware of the WHO IHR and its' requirement for an a priori assessment of the necessity for international notification
			Page 27, Line 19 This is unclear and warrants clarification. It gives the impression that biological incidents are frequent and not controllable, which is not the case. The type of biological incident that would necessitate a prepared international response plan is very rare. Indeed, since the introduction of the contained use directive in 2000, I'm not aware of any such biological incidents involving genetically modified organisms. The EC collects information on GM accidents and would be able to provide appropriate data to provide some necessary perspective.	The SCs agree with this comment and have deleted 'given the difficulties in preventing a biological accident of any type' and added **'In specific and high-risk cases'**, ….

41	Fears Robin, EASAC, robin.fears@easac.eu, United Kingdom	3.2. Major gaps in knowledge to be considered for performing a reliable risk assessment in the areas of concern	The first products from synthetic biology are very likely to fall within the scope of existing EU regulations and risk assessment frameworks for GMOs (H-J Buhk, Synthetic biology and its regulation in the European Union, New Biotechnology 2014 31, 528-31). It may not always be clear if a synthetic biology product falls under deliberate release or contained use regulations, for example if a GMO is confined within a secure casing but intended for use outside the laboratory as a biosensor (UK Parliamentary Office of Science and Technology publication No. 497, May 2015 "Regulation of synthetic biology", http://researchbriefings.files.parliament.uk/documents/POST-PN-0497/POST-PN-0497.pdf). EASAC reiterates our previous recommendation that innovative products should be regulated according to their traits rather than the technology used to generate them. This focus on trait/product-based regulation is increasingly being debated elsewhere in the EU (for example, see discussion in UK Parliamentary Office of Science and Technology publication cited in previous paragraph). We recommend that the European Commission leads discussion to explore what gaps in knowledge need to be filled in order to move from a technology-based to a trait-based regulatory framework. For citizen science, consistent with the quoted conclusions of Seyfried et al 2014 in the Opinion, the report from the UK Kings College London Workshop 2014 ("Synthetic biology and biosecurity: how scared should we be?, http://www.kcl.ac.uk/sspp/departments/sshm/news/synbiosecurity.aspx) also observes that any concerns associated with the assumed trend of "deskilling" reflect too simplistic a perspective.	The SCs agree with the comment. However, the SCs are committees independent from the EC.

42	Scott Deborah, Engineering Life project, University of Edinburgh, Deborah.Scott@ed.ac.uk, United Kingdom	3.2. Major gaps in knowledge to be considered for performing a reliable risk assessment in the areas of concern	p27 3.2 Major gaps – Genetic Parts – lines 38-41 and Opinion p36 lines 1-2) – While further development in "predictive tools" corresponding to those used in other engineering areas would be great, the SCs should also ask: What if such predictive tools are not possible for complex biological systems? If we cannot quantify or even identify all of the uncertainties posed by new biological systems, what other kinds of assessment and processes of consideration should we develop? Based on the work of social scientists engaging with uncertainties beyond quantifiable risk, additional questions for assessment could include: who benefits from the proposed action and who stands to bear the costs and risks; what degree of control affected communities have; what indirect effects may exist; what are potential blind spots and divergent scientific views; what alternatives exist (Wynne 1992; Peel 2004; Stirling 2007 & 2008). I cannot upload the Wynne and Peel articles as they are too large (really, they aren't _that_ long!). Their full citations are: Peel, Jacqueline. 2004. Precaution – A matter of principle, approach or process? Melbourne Journal of International Law 5:483-501. Wynne, Brian. 1992. Uncertainty and environmental learning: Reconceiving science and policy in the preventive paradigm. Global Environmental Change 2 (2): 111-127. I would be happy to send PDFs of those articles to anyone interested.	The SCs in this section of the text address the whole issue of knowledge gaps in risk assessment methodologies. A discussion on uncertainties is not included because these uncertainties will be a part of a risk assessment and is beyond the scope of this Opinion.
43	Sanders Dale, John Innes Centre, Dale.Sanders@jic.ac.uk, United Kingdom	3.2. Major gaps in knowledge to be considered for performing a reliable risk assessment in the areas of concern	We do not feel that the Opinion adequately addresses regulatory frameworks for organisms edited using genome editing. The application of genome editing technologies might lead to a lack of traceability, so there should be consideration of how chain-of-custody can be strong for regulatory and consumer choice purposes. Modification by genome editing can result in organisms that do not contain any inserted genetic material, and in some cases with only, for example, a single point mutation. Regulation of such GM organisms is not addressed.	The SCs aimed at pointing to the use of technologies for DNA synthesis and genome editing involving TALEN, CRISPR and other engineered nucleases but also to the approach known as Multiplex automated genome engineering (= MAGE). This is clarified in the Opinion and references were added.

44	EuropaBio, d.carron@europabio.org, Belgium	3.2. Major gaps in knowledge to be considered for performing a reliable risk assessment in the areas of concern	P27, line 34-41 As noted on page 24 lines 27-34, there are established GMO risk assessment frameworks that consider emergent properties. The emphasised "major gap in knowledge" throughout the Opinion should be balanced against the fact that major regulatory bodies such as EFSA and ZKBS have issued opinions on synthetic biology and there is more than 30 years of international experience in identifying risks associated with GMOs, and that the principles of these frameworks are applicable to assessing entities created with the use of synthetic biology approaches. While predictive tools might assist with hazard identification, these are not indispensable for risk assessment.	The mandate required the SCs to address gaps in knowledge. There are emergent properties of SynBio that may require new risk assessment methodologies and these are reported in this Opinion. However, these do not dispute the GMO experience.
			P27, line 35-36 Also page 37 Table 3 "Tools for predicting emergent properties of complex biological systems may not be sufficiently accurate or may not be available to risk assessors" This statement falsely implies that complete and accurate knowledge is necessary in order to be able to conduct a risk assessment and formulate risk management strategies. This is not the case in GMO risk assessment, where scientific uncertainty is a factor considered in identifying data requirements and determining appropriate risk management strategies. Suggested rewrite: "Currently, the tools for predicting emergent properties for highly complex biological systems created with SynBio approaches may not be comprehensively developed for use by risk assessors." It should also be noted in these sections that this does not prevent risk assessment or the development of risk management strategies.	While the SCs acknowledge that there is uncertainty in the risk assessment, nevertheless the SCs recommend that risk assessors use complete and accurate tools for their risk assessments.

			P28, line 1-3 Comparative risk assessment is just one way of performing risk assessment, therefore the lack of suitable comparators is not a challenge in risk assessment per se and this needs to be reflected in the text. Suggested edit: "While comparative risk assessment is typically utilised to assess the safety of a novel organism, the lack of suitable comparators for some synthetic biology organisms can be addressed by applying alternative risk assessment approaches." In addition, this very much depends on the organism and comes back to the definition. If it is really radical changes that has been made this is true but if it is just new methods that have been used for the modification it is actually the other way around because you can control and limit the changes you make significantly.	The mandate required the SCs to address gaps in knowledge. There are emergent properties of SynBio that may require new risk assessment methodologies and these are reported in this Opinion. However, these do not dispute the GMO experience such as with comparative assessment.
			P28, line 4-12 Efforts to improve data standards is welcomed. The text remains, however, unclear in which circumstances this data needs to be collected – is it envisaged for contained use, or for applications that might have commercial applications or may be released in the environment? Furthermore, how would such data be of use to risk assessors? Lastly, it remains unclear why the role of national structures is ignored or not properly described here and why no recognition is given to already established biosafety processes that successfully support laboratory research in the area of synthetic biology? Suggest to edit the paragraph taking into account good biosafety practices that are already established and work well.	Should apply to all genetic constructs that use genetic parts, irrespective of the type of use. Collecting this information in a standardised form will also help risk assessors to learn faster about real world consequences and to update and adjust assessment practices.
45	EuropaBio, d.carron@europabio.org, Belgium	3.2. Major gaps in knowledge to be considered for performing a reliable risk assessment in the areas of concern	P30, line 25-26 We believe that the following text is self-contradictory and should be deleted "The second shortcoming is the lack of standardised media to test the escape frequencies for several potential escape environments". Whilst measuring escape frequencies is of course possible, in the case of escape, the SynBio organism would be oblivious to whether the media are standardised or not. Therefore if it is not known which media are most meaningful or which factors might favour escape, in our view, there would be little value in standardization.	The SCs do not agree. The point is that different engineered auxotrophies could lead to different escape frequencies in different types of media. The challenges is to simulate a number of possible media the strain could accidentally be released to and see if it survives on any one of these media. Standardisation gives applicants and risk assessors a clear and objective perspective on more realistic escape frequencies. No change in the Opinion is needed.

			P30-31, line 36-4 This is not relevant for most formats that can be envisioned. It is true that many combinations can be tested, but only one will be selected for actual technical use and that can be risk assessed in the classical way.	The mandate required the SCs to address gaps in knowledge. There are emergent properties of SynBio that may require new risk assessment methodologies and these are reported in this Opinion. However, these do not dispute the GMO experience
			P30, line 39 We do not understand why the case-by-case approach may no longer be feasible for genome-wide modifications. Any potential risks associated with new products would derive from the product characteristics and not from the process used to make it. We encourage a product-based, not a process-based risk assessment approach.	The scale and speed at which new and complex organisms will be generated (first anticipated within the context of contained use activities) might considerably increase administrative burden and efforts to perform assessments on a case-by-case basis, at least if one sticks to the approach that a molecular characterization should be performed for every single genetic modification and that the potential effect of each of these genetic modifications on product characteristics needs to be assessed. (A possible way forward would be to distinguish between applications that necessitate a comprehensive risk assessment and those applications that can generally be regarded as safe). The text was edited to clarify this.

			P30, line 39-42 "The use of genome editing methods in a multiplexed fashion allow the simultaneous generation of larger number of variants, the genome-wide modification of organisms and a more pervasive change to the genomes of living organisms than those obtained by traditional genetic modification techniques" Comment: The sentence is factually incorrect. For example, a well established and "traditional" method of genetic modification such as chemical mutagenesis will result in "simultaneous generation of larger number of variants, genome-wide modifications and pervasive changes to the genome of the living organisms". Suggested edit: "The use of genome editing methods in a multiplexed fashion theoretically may allow the simultaneous generation of large number of variants, the genome-wide modification of organisms and a more accurate and precise change to the genomes of living organisms than those obtained by traditional genetic modification techniques."	The SCs agree with the comment and have edited the text as follows: "The use of genome editing methods in a multiplexed fashion theoretically may allow the simultaneous generation of large number of variants, the genome-wide modification of organisms and a more accurate and precise change to the genomes of living organisms than those obtained by traditional genetic modification techniques according to current regulations."
			P30-31, line 42-44, 44-46, 1 How is a case-by-case risk assessment "hampered" or "no longer feasible"? These presumptions need to be substantiated with examples. Is this in case where release of multiple modified organisms (tens? or hundreds?) is planned? There may be new challenges with Synthetic Biology, but a GMO case-by-case risk assessment can be adapted according to the characteristics of the organism.	See response above
			P31, line 1-4 "With respect to GMM deliberately released into the environment, there is a lack of experience on the characterisation at the genetic or molecular level of the organisms necessary/relevant for an adequate appreciation of the risk these microorganisms may confer." In our view it is unclear what is meant by this passage as everything is dependent on the type of genetic modification made and its extent. In addition, microorganisms can be easily genome-sequenced thus characterization at the genetic and molecular level is possible. We therefore suggest to delete the sentence.	The SCs agree with the comment and will delete this sentence in the text.

46	Paton Michael, Health & Safety Executive, michael.paton@hse.gsi.gov.uk, United Kingdom	3.2. Major gaps in knowledge to be considered for performing a reliable risk assessment in the areas of concern	Page 30, Line 3 The tools and methodology for semantic containment proposed for synthetic organisms appear to be more robust than those currently used. Such tools, depending on their robustness, may allow some work currently undertaken in laboratory conditions to be done without physical containment. For instance, one obvious application would be generating model organisms such as C. elegans or Drosophila that are dependent on artificial nucleic acids or other xenobiological compounds. Such model organisms could then be studied with little or no physical containment in the knowledge that there was no possibility of their survival outside of controlled laboratory conditions.	The SCs theoretically accept this comment. However, the semantic containments should be better understood and investigated before physical containment can be relaxed.
			Page 31, Line 1 The application of gene drive technology is an important area for further research to ensure the benefits are realised in a safe manner. Further research to address potential unpredictable ecological consequences has been proposed by some scientists (Akbari et al (2015) Science, 349, 927-929)	The SCs do not consider "gene drives" as falling under the definition of SynBio, as "the application of science, technology and engineering to facilitate and accelerate the design, manufacture and/or modification of genetic materials in living organisms". The methods used are related, but "gene drives" aim at modifying the genetic composition of populations, not of individual organisms; a full analysis of the risks and implications of "gene drives" would be outside the scope of this Opinion. We have, however, clarified in the text that this technology needs further analysis.

47	Fears Robin, EASAC, robin.fears@easac.eu, United Kingdom	3.3. Research recommendations on the main scientific gaps	It would be helpful for the Opinion to include additional strategic discussion of the shared priorities for a research agenda – spanning all synthetic biology methodologies – on the environmental implications, for example as published in the work of the Woodrow Wilson Center (Drinkwater et al 2014, "Creating a research agenda for the ecological implications of synthetic biology", http://www.synbioproject.org/process/assets/files/6685/_draft/synbio_res_agenda.pdf). Significant points are sometimes dispersed throughout the Opinion but need to be brought together into a coherent agenda that includes the fundamental questions that apply to all, or most, of the foreseeable outputs from synthetic biology research (as discussed in detail in the Woodrow Wilson Center report): (i) What are the comparators for risk assessment, particularly when multiple traits may be involved? (ii) What are the priority characteristics to be assessed when phenotyping novel organisms? (iii) What are the key elements that contribute to interaction with the environment, for example, fitness, genetic stability, lateral gene transfer? (iv) What are the intrinsic and external controls for the novel organisms? (v) How feasible will be monitoring, and who does it? (vi) What modelling tools can be used before release into the	Thank you for your opinion. Rearranging the Opinion from the current text in which the SCs address the issues based on the SynBio subfield, would not provide more clarity.

			environment? (vii) What research is needed to standardise testing methods, data reporting, and organism characterisation and who is responsible for developing, promoting and enforcing standards? EASAC recommends a systematic approach to identify particular research priorities for the foreseeable future within a coordinated strategy customised according to progress anticipated in the different methodologies. This strategy requires increasing interaction between researchers and those regulating and enabling the use of synthetic biology and within the broader context of promoting engagement between the scientific community and the public. We also recommend that the development of future EU research programmes takes account of the research topics identified in section 3.3 in order to fill knowledge gaps and to be able to assess risks on a better scientific basis. We recommend that the methods of Systems Biology will be useful in helping to characterise new micro-organisms modified with complex gene constructs. We support the suggestion in the Opinion that it would also be useful to establish a public repository for well-characterised engineered components particularly those embedding new safety features.	

48	Sanders Dale, John Innes Centre, Dale.Sanders@jic.ac.uk, United Kingdom	3.3. Research recommendations on the main scientific gaps	We strongly support the need for research to allow advancement of the risk assessment process, in particular to develop the risk assessment process such that it can advance as new types of modifications are found to be low risk and no longer require such stringent assessment. We would also support, as highlighted within the document; the design of safer biosystems with new forms of biocontainment that are appropriate to the activities being conducted. Consideration of the use of existing GMOs with a proven safety record as acceptable comparators for risk assessment of more complex modifications (Page 9, lines 5-7) is a sensible step forward and would allow the choice of comparators to advance along with the risk assessment process. It is vital to move the risk assessment process forward appropriately as scientific knowledge increases. In all risk assessment it is also important to fully consider benefit alongside risk. We recommend that guidelines be presented as giving an 'acceptable level of risk' rather than using the term 'safety'.	Thank you for your comments and recommendation. However, the SCs consider that safety implies 'acceptable level of risk'.
			Page 30, lines 44-46 acknowledges that a case-by-case risk assessment, as currently adopted for living organisms obtained by traditional genetic modification techniques, may no longer be feasible. This again highlights the need for research to establish appropriate risk assessment that it able to respond to rapid advances in technologies and knowledge.	Thank you for your comments.

49	Cannell Martin, Defra, martin.cannell@defra.gsi.gov.uk, United Kingdom	3.3.1. Research recommendations related to gaps in the six novel SynBio developments	Page 32, Line 34 Further work is required on designing synthetic constructs and microbes to be intentionally out-competed over time. For this research to progress, more quantitative data are needed on how GMMs perform in sample environments (Wright et al., 2013). The current lack of in-depth testing results in difficultly in accurately assessing which safety mechanisms and designs are best at preventing ecological invasion and horizontal gene transfer. It will be important to ensure that data gathering on how GMMs perform in sample environments is strongly linked to the emergence and risk assessment of real-life products. There has been a tendency for some GM regulators to repeatedly request additional data on environmental interactions, which results in evidence that is only of academic interest and is not helpful to the risk assessment process. Such research is often misguided and poor value for money in terms of the extent to which it helps address key risk issues.	The SCs consider that there is a lack of evidence supporting this opinion and therefore, no changes have been made.
50	EuropaBio, d.carron@europabio.org, Belgium	3.3.1. Research recommendations related to gaps in the six novel SynBio developments	P31, line 27 Under genetic parts the first priority for further research seems to be "Research to characterise the function of biological parts". This could imply that researchers do not understand the functions of the genetic parts that they are using which we would dispute since particular parts are deliberately used for their known functions.	The SCs agree with this statement and have edited the text accordingly, clarifying that this bullet addresses interactions between parts..

			P31, line 33-37 The text is unclear about what is being addressed: contained use, industrial application or environmental release. In addition, it is necessary to differentiate between areas of biotechnology that will be affected by such data requirements (presumably certain synthetic biology applications) and these that will not (traditional genetic engineering?).	The SCs agree with the comment and the Opinion text has been modified on P31 line 33-37 : reasonably it can be assumed that industrial applications and environmental releases will be preceded by contained use applications. However, the SCs agree that more clarification should be made on the level of data required depending on the intended use (contained use versus deliberate release). The edit reads as follows: Line 33-35 'research approaches to streamline …., including systems biology models. The level of detail of data to be provided should take into account the intended use (contained use versus deliberate release into the environment).
			P31, line 40-41 We support and encourage the use of GMOs with a proven safety records as acceptable comparators for risk assessment.	Thank you for your support.
			P32, line 14-15 "The current consensus is that the bare minimum of safety for a deployed genetically 14 modified microorganism (GMM) should consist of multiple safety devices of different 15 types (Presidential Commission for the Study of Bioethical Issues, 2010)." We believe that whilst this claim may be valid (currently) for some products of SynBio, it is definitely not applicable for industries' uses of synthetic DNA constructs and we believe that a clear distinction should be made.	The SCs agree and have modified the Opinion text: P32 – line 14-15: 'The current consensus is that the bare minimum of safety for a deployed genetically modified microorganism (GMM) for intentional environmental release (commercial, experimental or environmental purposes) should consist of multiple safety devices of different types (Presidential Commission for the Study of Bioethical Issues, 2010)."
51	Paton Michael, Health & Safety Executive, michael.paton@hse.gsi.gov.uk, United Kingdom	3.3.1. Research recommendations related to gaps in the six novel SynBio developments	Page 31, Line 24 Currently only five of the six novel SynBio developments are discussed in this section. Assuming gene drive falls into the area of DNA synthesis and genome editing, as identified in Table 3, research priorities in this area should be discussed.	The SCs indeed do not consider "gene drives" as falling under the definition of SynBio, as "the application of science, technology and engineering to facilitate and accelerate the design, manufacture and/or modification of genetic materials in living organisms". The methods used are related, but "gene drives" aim at modifying the genetic composition of populations, not of individual organisms; a full analysis of the risks and implications of "gene drives"

				would be outside the scope of this Opinion. We have, however, clarified in the text that this technology needs further analysis.
52	Elbing Kerstin, German Life Science Association (VBIO e. V.), elbing@vbio.de, Germany	3.3.1. Research recommendations related to gaps in the six novel SynBio developments	P31, line 33-37 It is not clear to us, what exactly is addressed by this bullet point: contained use, industrial application or environmental release? Suggested edit: The SCs should specify the scope of this bullet point.	The SCs agree with the comment and the Opinion text has been modified on P31 line 33-37 : Reasonably it can be assumed that industrial applications and environmental releases will be preceded by contained use applications. However, the SCs agree that more clarification should be made on the level of data required depending on the intended use (contained use versus deliberate release). The edit reads as follows: Line 33-35 'research approaches to streamline …., including systems biology models. The level of detail of data to be provided should take into account the intended use (contained use versus deliberate release into the environment).
			P32, line 16 The SCs suggest the establishment of a public repository of well characterised engineered safe chassis and safety devices as such a public repository might help to minimize risks. We hesitate to support this suggestion before all relevant stakeholders agreed upon a clear concept as to how this repository is organized and managed, how IP rights should be handled, etc.	Thank you for your comment. The SCs agree and changed the text accordingly.
			P32, lines 25ff We are well aware that while adding modules might make the chassis less fit, increasing bioreactor robustness might also increase environmental robustness. We also see the demand for additional research to establish the best approach to deal with this trade-off. But as of principal reflections we want to underline that in practise there is no complete escape from this dilemma. Limitation of the trade-off will be an approximation only.	The SCs agree with this comment. However, this is beyond the mandate.

			P32, lines 31-32 As a matter of transparency we ask the SCs to exemplify, which level of regulation is intended and which time frame has to be expected. We want to express our view that acceptance of these standards will be higher, if they are lean and a direct safety benefit can be seen.	The SCs agree with the comment. However, this is beyond the mandate.
			P32, line 42 We like to emphasize that there is a trade-off between the demands of increased genetic robustness and decreased environmental robustness, which can not be solved completely. We therefore suggest that further research should not alone focus on quantifying evolutionary change, but in addition should include „qualifying" measures of evolutionary change as well.	The SCs agree and will change the text to "Further fundamental research on quantifying and qualifying …"
			P34, line 14 VBIO already expressed in its statement on preliminary opinion II that the inclusion of Citizen Science (e.g. Do-It-Yourself Biology - DIY Biology) seems misguiding as it is neither a technology nor a method of engineering. Citizen Science is specified by the person doing science (Synthetic Biology) in a certain framework of facilities in the absence of a professional research infrastructure. We agree that DIY Biology raises questions on training, safety, security, compliance and supervision that need to be addressed. We would have preferred a longitudinal approach including special considerations about Citizen Science in the recommendations wherever necessary und useful. The SCs recommend the development of strategies to further increase and maintain the compliance of citizen scientists with national biosafety rules and codes of ethics, including collaboration with traditional institutions and training. As a matter of transparency we ask the SC to exemplify, who should promote this strategic process, which stakeholders to include, what level of regulation to achieve and which time frame to expect.	The SCs are aware that DIY Bio is not a technique. Therefore, the chapter was included in a section called "accessibility". The SCs considered it best to have it contained in one section rather than to divide the text between chapters. The level of detail requested is beyond the scope of this Opinion.
53	European Federation of Biotechnology European Federation of Biotechnology, European Federation of Biotechnology, karsten@efb-	4. OPINION	Opinion comments submitted on behalf of the European Federation of Biotechnology. Pg 35, lines 15-18 The European Federation of Biotechnology (EFB) objects to suggestions that more general problems	The SCs refer to the response to comment 18 above.

	central.org, Spain		would be addressed because of or linked with SynBio: whilst demand for feedstock by SynBio may put pressure on land this is not a problem unique to SynBio; the removal of biomass from agricultural land resulting in decreased soil fertility has been an issue for the past several thousand years.	
			Pg 35, lines 21-25 The European Federation of Biotechnology (EFB) objects to suggestions that more general problems would be addressed because of or linked with SynBio: traditional selection techniques performed by farmers and breeders produce new strains, thereby replacing older ones; again, this is not a new problem brought about by SynBio.	The SCs refer to the response to comment 18 above.
			Pg 35, lines 25-29 While de-extinction may fit into the very broad definition of SynBio as stated in the Opinion I Document EFB would not describe this as a SynBio application; it would be more akin to cloning plus some DNA synthesis.	The SCs refer to the response to comment 18 above.
			Pg 35, lines 33-34 EFB signals that this is a rather vague statement; attempts to find the reference for this failed, the only ETC reference in the bibliography is "ETC Group (2010) The New Biomassters: Synthetic Biology and the Next Assault on Biodiversity and Livelihoods. Montreal: ETC Group." (sic).	The SCs agree and have deleted this sentence.
			Pg 35, lines 35-36 This statement may be true, however the references for this are the aforementioned somewhat partial "Synthetic Biology and the Next Assault on Biodiversity and Livelihoods" reference and a book that could not be consulted. EFB stresses that many if not all industrial SynBio projects strive for sustainability as that is one of the major selling points of the technology. Additionally, even if this were not the case, there are other advantages of SynBio over traditional chemical processes, such as cost-effectiveness and there not being a need for harsh solvents. Summary for "Impacts on biological diversity and conservation" EFB stresses that many of the points in this section are not unique to SynBio, and some are not applicable at all. While the accidental release of GMOs into the environment should be assessed for the potential risks posed, we see no justification for saying that SynBio would	While the biotech industry attempts to market SynBio as a step towards sustainability, this is not automatically the case. There are many counter-examples: massive land use change for biofuels, engineered bacteria to clean up after mining or oil sand extraction, conversion bacterial to feed on methanol derived from fossil gas, even bioplastics are not necessarily compostable (only the source can be bio). The list is very long.

			affect conservation efforts and biodiversity over and above any other new technology, or indeed any traditional agricultural practices.	
			Pg 36, Table 2: Protocells Protocells, as defined in the document, do not fit the SynBio definition from Opinion I, being neither alive nor containing any genetic material to modify. EFB proposes to class these as products or tools of SynBio for the present, and re-asses the technology at the end of the proposed time frame (2020).	Protocells are considered part of SynBio research and therefore were included in the Opinions. The time frame is 2025.
			Pg 37, Table 3: Genetic parts, point 2 A standardised genetic parts library with part characterisation would be very useful not just to regulators but researchers as well, and is something that should be vigorously pursued.	Thank you for your comment. The SCs agree.
			Pg 37, Table 3: Minimal cells and designer chassis The ability to design a chassis robust enough not to be subject to evolution is certainly a major gap in our knowledge. However this may not be desirable in all cases as some techniques may involve forced evolution and it should still be possible to accomplish this with our chassis.	Thank you for supporting our recommendation. The SCs agree with this comment. Engineering and evolution could be performed on chassis or non-chassis organisms. And the risks outlined for chassis organisms are also risks for non-chassis organisms that are engineered.
			Pg 39, lines 1-5 EFB supports this proposal: this database should also make it easier for researchers to share bioparts and data on bioparts.	Thank you for your comment. The SCs agree.
			Pg 39, lines 8-13 EFB encourages sharing and building on experience: as we learn how safe or risky each GM organism is this should inform future assessments rather than relying on an inflexible baseline.	Thank you for your comment. The SCs agree.

54	European Federation of Biotechnology European Federation of Biotechnology, European Federation of Biotechnology, karsten@efb-central.org, Spain	4. OPINION	Pg 40, lines 37-42 While unintentional release should be prevented it is unclear why so many new forms of biocontainment are needed; the case has not been made here that organisms produced using SynBio techniques are any more dangerous than "traditional" GMOs, nor that their biological features would necessitate containment measures so far unavailable.	Additional biocontainment devices should allow for more flexibility in choosing restriction in the use of novel organisms. It could either replace current forms of containment or add additional layers of safety to more dangerous cases.
55	EuropaBio, d.carron@europabio.org, Belgium	4. OPINION	P35, all page The risks that are being addressed here are not specifically related to synthetic biology – that is a common potential risk from any use of biotechnology.	While the biotech industry attempts to market SynBio as a step towards sustainability, this is not automatically the case. There are many counter-examples: massive land use change for biofuels, engineered bacteria to clean up after mining or oil sand extraction, conversion bacterial to feed on methanol derived from fossil gas, even bioplastics are not necessarily compostable (only the source can be bio). The list is very long.
			P35, line 21 Need to insert the word 'plant' before 'varieties'.	The SCs agree with this edit.
			P35, line 25-29 Suggest to delete the paragraph as de-extinction is out of scope and not a realistic issue, especially in the time frame until 2020. "Likewise, de-extinction…..affect Aichi targets 1 and 13."	It is noted that the timeframe of the Opinion is 10 years from now. A main point here is that there is an on-going discussion about the prospect of de-extinction in the long-term future, which might have a negative impact on current conservation efforts. The text was adapted to make this clear.
			P35, line 33-34 Highly speculative and needs to be supported by a credible example if kept in the text, otherwise suggest to delete P36, line 1-2 The probability and impact of the risks needs indeed to be taken into account. This point should be emphasised more in the text.	The SCs agree with this edit and will delete this sentence in the text.
			P36, table 2 Comment to "genetic parts": Why do the scientific committees assume increased frequency of use of uncharacterised components? How does this compare with sequences mutated by chemical mutagenesis? Where is the difference that supposedly can challenge risk assessment?	The SCs emphasise that there can be an increase in genetic parts that are not characterised for their risk safety.

			P36, line 11 These recommendations would actually lead to more radical solutions where the predictability is much lower than for the changes that the industry currently make.	There is no explanation for this statement and thus, the SCs are unable to comment.
			P37, line 8-10 Mitigation of risks begins at local level, however this document is not making sufficient reference to biosafety practice for containment and mitigation. This needs to be added in the final version of the text.	See response on comment 37
			P38, table 3 On genetic parts: This is true for all modifications that has been made up to date. This is no different for parts that might be classified as synthetic biology DNA synthesis and genome editing: The statement "Lacking risk assessment for organisms with pervasive changes to the genomes produced by MAGE/CRISP/zinc finger protein techniques." is factually incorrect. CRISPR/Zink finger/Talens are just ways of securing very precise changes at the genome at the exact spots where you want it. It is actually easier to risk assess than traditional methods. If you go into a MAGE format you will create big libraries of organisms with multiple chenges, but you will among that library isolate one preferred candidate and do genome sequencing of that. So you will know exactly which changes was introduced and you can risk assess each of those in exactly the same way as for changes made my other methods. You can actually make a more thorough risk assessment compared to organisms made by classical evolutionary approaches as all mutations accumulated are random and typically there are so many of them that even after sequencing you cannot make a rational analysis. Suggested edit: delete this entry. "The methods for submitting genetic modification data and genetic parts information to risk assessors is yet unstandardised across EU member states and internationally, …" We believe that this is a question of perception since, to our knowledge, the EU has implemented a harmonized approval process, clearly providing guidance on the type of information required to describe and characterize the genetic modifications applied. Suggested edit: delete this entry.	The entry in Table 3 is referring to editing techniques in general and not as specific as provided in the comment. Therefore, the SCs cannot agree with the conclusion and have not deleted this text. Table 3 refers to methods for submitting genetic modification data and genetic parts information, which are as yet not standardised, despite the harmonised approval process.

56	EuropaBio, d.carron@europabio.org, Belgium	4. OPINION	P38, line 23 Undefined abbreviation used – 'RA' (for risk assessment).	Thank you for your comment. This will be corrected in the Opinion.
			P38, line 26-27 "Biosafety clearing house of bioparts" is presented as a recommendation of a way to improve risk assessment. How is this information going to help risk assessors? What kind of information will be needed and at what level in the R&D process is it supposed to be made available to risk assessors? How is this proposal contributing or improving current arrangement for biosafety?	The more complete the information on parts used is, the easier for the risk assessor to make a decision. Right now these parts registries have none or only rudimentary characterisation of safety relevant features.
			P39, line 1-5 The document contains several claims such as "Research approaches to streamline and standardise the methods for submitting genetic modification data and genetic parts information to risk assessors across EU member states. Ideally, such information should be submitted in computable form to facilitate transparency with all stakeholders, and to enable the application of the aforementioned prediction tools, including systems biology models." From our perspective this would endanger the distinction between standard information and commercially confidential information and suggest that such an individualistic approach to risk assessment should be discouraged.	The SCs agree to change the text to "…to facilitate transparency with all stakeholders involved in the risk assessment process, …".
			P40, line 1-6 "Each individual chemical class of xeno-compounds (e.g., HNA, GNA) should initially be characterised and tested comprehensively (e.g., for toxicity and allergenicity), but in the future, in case of a proven safety record of particular classes of xeno-compounds, applications of such classes should be tested similarly to classical DNA modifications, namely based on a case-by-case assessment of the modified genetic information only." From our perspective there is no rationale to exclude xeno-compounds from the possibility of having the risk of emergent properties and associated safety risks, as implied in the document for other uses of SynBio.	The SCs agree with this comment and have edited the text to include this point: Even when individual chemical classes of xeno-compounds have been tested for toxicity and allergenicity, etc., a risk assessment is needed for emergent properties.

			40, line 30-31 Add text (in bold) to existing sentence: 'Research on impacts…of Synbio organisms that are likely to cause harm…. P40, line 37-38 Add text (in bold) to existing sentence: "Research on containment strategies…. To organisms resulting from Synbio techniques when such organisms are classified as dangerous or may cause harm."	This comment does not include a precautionary approach and the SCs have therefore not edited the text of the Opinion.
57	Elbing Kerstin, German Life Science Association (VBIO e. V.), elbing@vbio.de, Germany	4. OPINION	P35, line 20 & P35, line 33-34 As a matter of consistency we suggest to add the relevant CBD references.	References were provided in the underlying section 3.1.3
			P35, line 21 Suggested edit: Please insert the word 'PLANT' before 'varieties'.	The SCs agree and have modified the text.
			P35, line 25-29 Suggested edit: Please delete this paragraph as „De-extinction" is beyond the time frame of this preliminary opinion.	A main point here is that there is an on-going discussion about the prospect of de-extinction in the long-term future, which might have a negative impact on current conservation efforts. The text was adapted to make this clear. The time frame of the Opinion is 2025.
			P35, line 35 We agree that "SynBio alternatives for chemical products and industrial processes might not per se be more sustainable than traditional products". But placing this general statement under the headline of "biological diversity and conservation" is entirely misleading as sustainability is much more comprehensive.	The SCs consider substitution part of sustainability issues and therefore consider it correctly placed.
			P36, table 2 Suggested edit: Protocells: Add "... might mutate OR BE HORIZONTALLY TRANSFERRED ..."	The SCs agree with this comment and will change the text accordingly.
			P36, line 20-22 Suggested edit: "However, no single technology reliably manages all biosafety risks and new approaches AND COMBINATIONS OF EXISTING AND UPCOMING NEW STRATGIES will be necessary (…)".	The SCs agree with this comment and will change the text accordingly.

			P38, line 25 A Biosafety clearinghouse mechanism on bioparts, devices and systems to support risk assessment of genetic circuits generated with biological parts, devices and systems might be useful in some fields of SynBio although it is not clear what kind of information has to be passed at what stage and in what detail. We would like to stress that acceptance of a Biosafety clearinghouse mechanism will be much higher, if structures are lean and linked to an existing international organisation.	The SCs consider this beyond the scope of the Opinion.
			P38, table 3 a) Genetic parts: The statements are not exclusive to SynBio b) DNA synthesis and genome editing: The statement "Lacking risk assessment for organisms with pervasive changes to the genomes produced by MAGE/CRISPR/zinc finger protein techniques." is not correct. These techniques are instruments to secure precise changes in the genome at exact spots. This makes risk assessment more easy compared with traditional methods of genetic engineering. Suggested edit: Deletion of this statement	a) Correct, but this Opinion is on SynBio. b) See response to comment 27. The text is edited accordingly.
			P39, line 15-17 It should be stressed, that there is a bottleneck in fundamental knowledge about functional mechanisms of biological parts and interactions between biological components. P40, line 10-14 Any threshold depends on the environment and the engineered system. Therefore the justification for setting 10-11 seems to be weak. Please provide a reference to scientific literature.	This has been addressed under 'genetic parts' The SCs agree with this comment and the calculations have been made more explicit.Tthe calculation behind the 10exp(-11) number is based on typical cell densities and fermenter sizes
			P 40; line 26ff The research recommendations are of high significance for the improvement of risk assessment. Having in mind that the research priorities given in this Opinion might have consequences for future resource allocation, we suggest to make it more explicit, how this additional recommendations relate to the recommendations of SynBio developments 1)-6). Furthermore, we see a need to prioritise within the chapter "additional research recommendations". We want to indicate a certain fuzziness between the research recommendations in the executive summary and in the opinion chapter. In the latter case, questions concerning differences in physiology, vertical or horizontal gene flow, survival, persistence, ecological fitness and the rate of evolutionary change are (only) subsets of research on the	The SCs considered the fuzziness between the research recommendations and the executive summary to be sure that they are one to one.

			impact of introductions of SynBio organisms into the environment.	
			P40, line 30-31 Suggested edit: "Research on impacts…of Synbio organisms THAT ARE LIKELY TO CAUSE HARM…." P40, line 37-38 Suggested edit: "Research on containment strategies…. To organisms resulting from Synbio techniques IF THEY ARE CLASSIFIED AS DANGEROUS OR MAY CAUSE HARM."	The SCs do not consider this edit acceptable because it does not take into account precautionary approaches.
58	Elbing Kerstin, German Life Science Association (VBIO e. V.), elbing@vbio.de, Germany	7. REFERENCES	Publications of NGOs that are campaigning against GMO or synthetic biology are cited under the headline „scientific literature" (e. g. ETC 2010, FOE 2010, FOE 2012). Please make transparent the character of this material in the reference list as well as on page 12. Please verify the reference list: 1) Some publications like ETC 2013 (page 14) and ETC 2013a (page 15) are cited but not included in the reference list 2)	These publications were considered valid sources and thus, cited. These citations were added to the reference list.
			Duplicate Page 51, 5-7: Presidential Commission for the Study of Bioethical Issues (2010). New directions: The 5 ethics of synthetic biology and emerging technologies. Washington DC. 6 http://bioethics.gov/sites/default/files/PCSBI-Synthetic-Biology-Report-12.16.10_0.pdf Page 53, 36-37: US Presidential Commission for the Study of Bioethical Issues (2010). New directions, Ethics of Synthetic Biology and Emerging Technologies. www.bioethics.gov	The SCs agree and the text was edited.
59	Strassheim Swantje, German Federal Office of Consumer Protection and Food Safety, Department Genetic Engineering, swantje.strassheim@bvl.bund.de, Germany	Question 10	Table 3: Major gaps in knowledge DNA synthesis and genome editing: The opinion identifies techniques such as MAGE/CRISPR/zinc finger nucleases as techniques leading to pervasive changes to the genome. We think that those techniques do not per se lead to pervasive changes, but in many cases only introduce slight changes that can be assessed using GMO regulations. This point (which does not come throughout the rest of the document) should be further explained.	See response to comment 50

60	Scott Deborah, Engineering Life project, University of Edinburgh, Deborah.Scott@ed.ac.uk, United Kingdom	Question 11	p40 lines 20-25 – I do not disagree with this recommendation, but it is not a recommendation relating to further research needs. On page 31, the section of citizen science seems to indirectly speak to a gap of research examining individuals and groups that fall outside of the official DiY biology groups.	The SCs agree with this comment and will edit the text accordingly: more research is needed to find out HOW TO increase awareness and compliance etc.
61	Paton Michael, Health & Safety Executive, michael.paton@hse.gsi.gov.uk, United Kingdom	Question 9	Page 35, Line 19 Accidental release is one means of potentially impacting on the environment, however the impact and extent is dependent on the hazardous properties of the organism involved and circumstances of release. Is this section indicating that there is a greater likelihood of an accident occurring for particular applications of SynBio? If so, what is the rationale for this conclusion (eg are there particular issues, challenges or gaps in containment or control measures such that they are not adequate?).	The SCs do not state in the Opinion that there is a greater likelihood of an accident occurring for particular applications of SynBio.