Results of the public consultation on the Scientific Committees' preliminary opinion on Synthetic Biology I - Definition

A public consultation on this opinion was open on the website of the EU scientific committees from 06 June 2014 to 21 July 2014. Information about the public consultation was broadly communicated to national authorities, international organisations and other stakeholders. In total 64 comments were received from 21 organisations or individuals.

Among the organisations participating in the consultation, there were universities, public health institutions, NGOs and public authorities.

Each contribution was carefully considered by the scientific committees and the scientific Opinion has been revised to take account of relevant comments. In a significant number of cases, outlined in this document, this resulted in changes and corrections in the Opinion.

The table below shows all comments received on different chapters of the Opinion and SCs' response to them. It is also indicated if the comment resulted in a change of the Opinion.

Comments received during the public consultation on the Scientific Committees' preliminary opinion on Synthetic Biology I - Definition

SUBMISSIONS				Scientific Committees Response
	Name of individual / organisation	**Table of content to which comment refers**	**Comment**	**Scientific Committees Response**
1	Fears Robin, European Academies Science Advisory Council, robinfears@aol.com, United Kingdom	1 BACKGROUND	EASAC has previously welcomed the positive attitude taken by the European Commission towards the opportunities presented by synthetic biology and it is important that this positive attitude is maintained. In our present response we focus mainly on issues relevant to definition and scope of the topic, and we look forward to contributing again subsequently in later phases of the consultation on benefit-risk assessment and research priorities.	Scientific Committees (SCs) thank European Academies Science Advisory Council for their comments. No changes to the Opinion are required in relation to the comments.
2	Grimm Frauke, Federal Agency for Nature Conservation (bundesamt für Naturschutz, BfN), GrimmF@bfn.de, Germany	1 BACKGROUND	Page 8, line 29 ff.: Considering that the WG was uncertain if SynBio was covered by existing legislation it is surprising that the SC came to the conclusion that SynBio is largely encompassed within these legislations. The reasons for both should be explained in more detail and thus disclose some uncertainties surrounding SynBio.	Thank you for this comment. The 'Working Group' in this section does *not* refer to the WG on Synthetic Biology, but to the NTWG. The text was clarified.

3	Elbing Kerstin, German Life Science Association (VBIO e. V.), elbing@vbio.de, Germany	1 BACKGROUND	German Life Science Association acknowledges that the European Commission has initiated a comprehensive discussion on Synthetic Biology. This discussion is aimed to found the position of EU to this complex field of research and possible application. It partly interferes with other fields of modern biology which are highly disputed within society. Therefore, the issue of Synthetic Biology (SynBio) should be discussed with sense of proportion, taking the time which is needed. We recognize that the EU Commission has already defined three milestones: Opinion 1 (definition), opinion 2 (risk assessment methodology, safety aspects) and opinion 3 (research priorities). Nevertheless the milestones are likely to interfere and we would like to strengthen the process character of the discussion. As Synthetic Biology is evolving very fast, any kind of definition (opinion 1) will remain preliminary (see also p. 5 28ff). This should be recognized in later stages of the discussion on opinion 1 and the following debates on opinion 2 and 3.	Thank you for your comment. SCs approached this issue by including the words acceleration and facilitation in the definition to address the evolution of the field and this will be reflected in the following SynBio Opinions.
4	Boyce Andy, BBSRC (on behalf of the UK Research Councils), andy.boyce@bbsrc.ac.uk, United Kingdom	1 BACKGROUND	Comment on lines 15 - 18: The precautionary principle in an important part of scientific risk management. However, the application of precautionary principle had a negative impact on GM research and application in the EU. If a strong statement as this is made it should be acknowledged that the precautionary principle has to be applied in a balanced and appropriate manner.	Thank you for this comment. The background reflects the current EC policy and it is not a task of the Scientific Committees to express an opinion on this policy.

5	Edmundson Matthew, University of Edinburgh, medmunds@staffmail.ed.ac.uk, United Kingdom	1 BACKGROUND	Page 8, lines 28-29 In my opinion SynBio is not in itself a 'gene modification technique'. This definition conflates SynBio with the tools used in it; SynBio utilises existing and new gene modification techniques with the goal of creating DNA constructs with modular, standardised parts, and it is these tools which should be the main focus of regulation rather than the concept of SynBio.	Thank you for the comment. SCs consider that SynBio *techniques* do differ from previous gene modification techniques, which summarises the conclusions of the NTWG. However, these tools are covered by the current EU GM regulations. The main focus of the Opinions is to address risk assessment in the field of SynBio.
6	Geertsma Robert, New & Emerging Technologies WG [installed by EC DG SANCO Medical Devices Unit], Robert.Geertsma@RIVM.NL, Netherlands	1.1 General introduction	The New and Emerging Technologies WG (NET), installed by EC, DG SANCO, unit Medical Devices, reports to the Medical Devices Expert Group (MDEG). See the following link for a description of both these groups: http://ec.europa.eu/health/medical-devices/dialogue-parties/working-groups/index_en.htm The topic of Synthetic Biology has been discussed in the WG in 2011 and 2012 in relation to the regulatory framework, and was flagged as a fast emerging field, which might challenge the current as well as the proposed future regulatory framework. Since then, the topic is followed by the NET WG at a somewhat lower level, however kept on the agenda in case new developments would be identified. The work of the SCENIHR WG had been identified as a new development. We would be happy to share our information with the SCENIHR WG, and would be interested to investigate possibilities for further exchange of knowledge and information. Please contact me, in my role as chair of the NET WG (Note: my regular affiliation is RIVM - National Institute for Public Health and the Environment).	Thank you for this invitation. The member of SCENIHR chairing the WG on SynBio has already contacted Dr Geertsma and he already sent some information from the NET MDEG WG. Further exchange is welcomed.

7	Horsfall Louise, University of Edinburgh, Louise.Horsfall@ed.ac.uk, United Kingdom	1.1 General introduction	Line 15-18 This statement is inaccurate and misleading. The terminology is indicative of an anti-technology agenda and it is especially worrying that this has been included in the first and introductory paragraph. The potential for synthetic biology to have any impact on biodiversity is hypothetical at best and many counter arguments can be made.	Thank you for this comment. The general introduction reflects the current EC policy. It is not the task of the SCs to express an opinion on this policy.
8	Horsfall Louise, University of Edinburgh, Louise.Horsfall@ed.ac.uk, United Kingdom	1.2 Legal background	lines 25-29 Clarification is needed here. SynBio is indeed a fast-evolving field but it is not a gene modification technique as is suggested by this sentence.	Thank you for this comment. Indeed, SynBio *techniques* differ from previous gene modification techniques. This text summarises the NTWG report.
9	KEPES François, francois.kepes@epigenomique.genopole.fr, France	3 SCIENTIFIC RATIONALE	Dear Committee, I fully agree on the view of SynBio as a collection of conceptual and technological advances (Abstract). This statement should be made more central to the operational definition of SynBio as it justifies why SynBio has consequences that spread to all application fields of biotechnology. However, in my view the highlighted and repeated definition of SynBio in the Opinion is rather poor. "SynBio is the application of science, technology and engineering". For which purpose? "to facilitate and accelerate the design, manufacture and/or modification of genetic materials in living organisms". For which purpose? "to alter living or non-living materials." For which purpose? No answer, end of definition. I do not wish to add my own definition, just to point out that this one is little-informative and frustrating. Another aspect is that it fails to convey the essential information that SynBio is by necessity a cross-disciplinary domain. In this Opinion SynBio is presented as extreme genetic engineering. How about the computer scientists who present it as extreme computer science? Or, much more equilibrated and truthful,	Thank you for your comments. The SCs believe that this thought is clearly expressed in the definition. For risk assessment purposes, the SCs needed to provide an operational definition derived from a working understanding of SynBio as a collection of conceptual and technological advances (described in Section 3.2). For an operational definition, the SCs consider it necessary to focus on actual activities, applications and products of SynBio, instead of on abstract concepts and metaphors. We therefore have refrained from including “purpose” in our definition. The definition given presents SynBio as a cross-disciplinary approach (“science, technology and engineering”). The SCs refrained from using conceptual aspects the operational definition and from defining SynBio in the context of the theories of the field. The SCs should clarify that protocells or bionanotech are in the domain of nanotechnology or chemistry as long as they don’t produce living organisms. They are

			how about presenting it as a new domain at the crossroads of biology and mathematics/computer science? This Opinion also suffers from self-contradiction on the important issue of SynBio's concrete outputs. They are twofold, in vivo SynBio: GMOs (well discussed); and in vitro SynBio: protocells/nanoparticles/etc. Protocells (but no other in vitro SynBio expression such as e.g. nucleic acid-based boxes with conditional lids for drug delivery/galenics) are discussed on page 15. Good but insufficient. Yet on page 27 it is stated that "SynBio as defined here excludes work on biological entities that are not capable of replication or of transferring genetic material". Well, a lot of the protocell work, in particular the applied one (galenics) and of the remainder of the in vitro SynBio is excluded by this statement. Thus, this exclusion statement on page 27 is at odds with the community understanding of SynBio and with the description on page 15 of protocells. Hope this is useful. Thank you for your attention. François KEPES http://www.issb.genopole.fr/~kepes/CVsynthbio.html http://www.biologie-de-synthese.fr/us-index.html	important preparatory work, contributing to the long-term aims of SynBio research, Although protocells (just like “naked” DNA molecules) are per se not alive, the potential of protocells as precursors to fully synthetic cells and its deployment to modify the capabilities of living organisms clearly qualify them as part of synthetic biology research. The text on protocells in section 3.3.1.3 was amended accordingly.
10	Van der Vlugt Cecile, National Institute for Public Health and the Environment (RIVM), cecile.van.der.vlugt@rivm.nl, Netherlands	3.2 Key general terms	line 4-12 Definitions for LO, LMO and GMO are presented as a key for defining synthetic biology. These definitions have their origin in the Cartagena Protocol on Biodiversity or in the EU Directives 2001/18 and 2009/47. However, the Cartagena protocol and the EU Directives are slightly different with respect to their definitions and differ particularly in the underlying techniques to be used or to be excluded. The Working Group is asked to explain why they use definitions from both the Protocol and the Directives? What aspects of these definitions are considered important for defining synthetic biology? Which definition (or element of the definition) is the most important for defining	Thank you for this comment. This section indeed presents key definitions for this Opinion. It is correct to state that they may differ in some aspects particularly regarding the inclusion and exclusion of techniques. The text on inclusion and exclusion criteria on page 28 makes reference to the pertinent definitions and answers these questions.

			synthetic biology?	
11	Kremser Annette, Project Management Juelich, a.kremser@fz-juelich.de, Germany	3.3 Scope and Definition	Dear officers, ERASynBio, the ERA-Net in synthetic biology, an initiative of 16 European funders plus the NSF of the US recently published a strategic vision for the responsible development of synthetic biology. This vision (http://www.erasynbio.eu/lw_resource/datapool/_items/item_59/erasynbiostrategicvision.pdf) touches several points of your request. We would be grateful to get into further dialogue with you on the specific issues. Further information can also be found on our website www.erasynbio.eu Kind regards, Annette Kremser, Coordinator	Thank you for this information. The Opinion now makes reference to the ERASynBio strategy on page 11 and under 3.3.2.2.
12	Fears Robin, European Academies Science Advisory Council, RobinFears@aol.com, United Kingdom	3.3.1 Main scientific developments	SynBio concepts, section 3.3.1.1; p.11, l.31 onwards We recommend that you add information about some very significant recent research advances, e.g. the construction of a synthetic yeast chromosome and of a semi-synthetic organism with expanded genetic alphabet (an example of orthogonality) – see the special collection of articles from the journal Nature (May 2014) on http://www.nature.com/news/specials/synbio-1.15137. Synthetic biology research areas, section 3.3.1.3; p.14, l.10 onwards In addition to the development of novel methodologies and applications, it is also vital to appreciate the great scientific importance of synthetic biology in helping to achieve better understanding of natural biological systems, because synthetic systems can be simplified to allow for experiments that would be too difficult to interpret if done in their full natural context.	Thank you for these references. They have been considered for Opinion 2. The importance of SynBio as a scientific tool is acknowledged and the SCs agree it is important to mention it in this Opinion. We have done so in Section 3.3.1.

13	Van der Vlugt Cecile, National Institute for Public Health and the Environment (RIVM), cecile.van.der.vlugt@rivm.nl, Netherlands	3.3.1 Main scientific developments	line 15 The sentence starts with 'For risk assessment'. As this opinion is aimed at formulating and underpinning a definition for synthetic biology, this sentence raises the question whether the definition is aimed at framing those areas of synthetic biology which should be regulated. If this is indeed the case, the proposed definition is in line with this assumption. The working Group is asked to clarify this in the opinion.	Thank you for this comment. The SCs agree with this point of view as the Opinion is aimed at framing those areas of SynBio, which may need updates of risk assessment methods (as expressed on page 30, last two paragraphs). The regulatory question was not part of the mandate.
14	Van der Vlugt Cecile, National Institute for Public Health and the Environment (RIVM), cecile.van.der.vlugt@rivm.nl, Netherlands	3.3.1 Main scientific developments	line 23 'manipulation' should be 'modification' in accordance to the EU directives.	Thank you for this comment. The SCs agree and have adapted the text as indicated.
15	Van der Vlugt Cecile, National Institute for Public Health and the Environment (RIVM), cecile.van.der.vlugt@rivm.nl, Netherlands	3.3.1 Main scientific developments	page 11, line 32 In the past years the terms 'genetic modification' and 'genetic engineering' have both been used to refer to the same area of biotechnology, i.e. genetic modification using recombinant DNA-techniques. Nowadays 'genetic engineering' is also used to refer to synthetic biology, as this developing discipline is regarded as the engineering of biology. By using the term 'genetic engineering' in the context of seeking a definition for synthetic biology, it can be confusing what is meant by 'genetic engineering': 'traditional genetic modification' or 'synthetic biology'. The working group is asked to clarify this difference in the opinion and/or to check the opinion on the uniform use of the terms 'genetic modification' and 'genetic engineering'.	Thank you for this comment. The SCs used the definition of genetic modification from Directive 2001/18/EC and 2009/41/EC. Genetic engineering in this Opinion refers in general to the techniques/methodologies used for genetic modification without making a clear distinction – in line with our definition – between techniques/methodology for GM and SynBio and has been added to section 3.2
16	Van der Vlugt Cecile, National Institute for Public Health and the Environment (RIVM), cecile.van.der.vlugt@rivm.	3.3.1 Main scientific developments	page 14, line 11 The research area is 'synthetic genomics' and not 'DNA synthesis'. DNA synthesis is a tool. Leaving out 'DNA synthesis' in this heading would also be in accordance with the Table on p. 27.	Thank you for this comment. SCs consider that DNA synthesis is a more formal term than synthetic genomics, which is used as a brand name by a USA company.

	nl, Netherlands			DNA synthesis is an important development to be assessed, even outside the context of synthetic genomics; the ability to rapidly generate new genetic parts is important, and work on this specific tool is also a research activity that needs to be considered. Therefore, we have continued to use the term DNA synthesis.
17	Van der Vlugt Cecile, National Institute for Public Health and the Environment (RIVM), cecile.van.der.vlugt@rivm.nl, Netherlands	3.3.1 Main scientific developments	3.3.1.3, page 15 On this page, protocells are named as one of the research areas of synthetic biology. As a bottom-up approach, protocells are constructed using chemical and physical approaches aiming at the development of living systems. As stated in the opinion, these systems are currently not 'alive' – i.e. are not in line to the definition of a living organism. Being 'alive' seems however an important element of the proposed definition for synthetic biology. It is unclear whether the exclusion of protocells, as a research area of synthetic biology, from the definition is an explicit choice of the Working Group. We suggest that this choice should be clearly explained in the opinion as the current definition is not covering protocells. As a note, developments like DNA origami and protein engineering are also research areas generally recognized as synthetic biology. These research areas are also not covered by the proposed definition for synthetic biology.	Thank you for this comment. For clarification, protocells and bionanotech are in the domain of nanotechnology or chemistry as long as they do not produce living organisms. They are important preparatory work, contributing to the long-term aims of SynBio research. Although protocells (just like "naked" DNA molecules) are per se not alive, the potential of protocells as precursors to fully synthetic cells and its deployment to modify the capabilities of living organisms clearly qualify them as part of synthetic biology research. SynBio research is much broader and also includes activities that are not biology at all, such as developing software and databases. The text on protocells in section 3.3.1.3 was amended accordingly.

18	Boyce Andy, BBSRC (on behalf of the UK Research Councils), andy.boyce@bbsrc.ac.uk, United Kingdom	3.3.1 Main scientific developments	Comment on page 13 line 21: There are over 10,000 parts in the registry: http://parts.igem.org/Catalog Comment on page 14 line 10: Bionanoscience is an important area of synthetic biology which is missing from this list. The UK alone has funded more than £20,000,000 of synthetic biology research in this area including the new multidisciplinary research centre at the University of Bristol: http://www.bbsrc.ac.uk/news/research-technologies/2014/140130-pr-new-synthetic-biology-research-centres.aspx	Thank you for these comments. The exact number currently is 10,340. While Bionanoscience is bordering SynBio, connecting it to nanotech, it is not defined as part of SynBio, thus, we have not included it in our definition.
19	Fears Robin, European Academies Science Advisory Council, RobinFears@aol.com, United Kingdom	3.3.2 Regulatory aspects (GMO-regulation, Convention on Biodiversity)	Regulatory aspects in the European Union, section 3.3.2.1; p.15, l.38 onwards In some general respects, consideration of good practice on regulatory issues for synthetic biology – when not specific to GMO regulations – can learn from previous evaluation of the issues for nanotechnology and other emerging technologies. For example, there are general issues relating to the implementation of principles and practices to underpin a structured approach to assessment of benefit-risk and understanding how to develop models in vitro to predict activities in vivo. The principles and procedures for determining the impact of engineered nanomaterials on human health and the environment are discussed in further detail in the EASAC-JRC report in 2011 (see http://www.easac.eu/home/reports-and-statements/detail-view/article/first-joint.html). In drawing on the lessons learnt from consideration of benefit-risk assessment for other technologies, it is essential to engage with the public and to clarify ethical and social concerns. The scientific community must proactively communicate a balanced account of progress, opportunities and uncertainties while, at the same time, raising public awareness about the established regulatory frameworks that evaluate effects on health and the environment. It is worth observing that in the 2010 European Commission survey of public attitudes across Europe, the	Thank you for your comments. We agree that consideration of good practice on regulatory issues for synthetic biology can learn from non-GMO regulations, e.g. nanotechnology and other emerging technologies and understand that benefit-risk assessment for other technologies is important and consider that synthetic biology should be governed according to the evidence relating to risks and benefits. We appreciate the information about the upcoming updates from EASAC on synthetic biology and agree that it is important that synthetic biology is covered in the already available legislation and risk assessment that is embedded within the current procedures for GMOs and biotechnology. The Opinion has been amended accordingly.

			majority of respondents agreed that synthetic biology should be governed according to the evidence relating to risks and benefits, rather than moral concerns. Official statements and recommendations on SynBio in Europe, section 3.3.2.2; p.18, l.18 onwards. We appreciate the citing of our previous (2010) EASAC report on synthetic biology and our more recent work (2013, cited on p.17, l.38) on GM applications in agriculture. Later this year, EASAC will be updating and extending our work on synthetic biology to take account of recent scientific advances and policy developments, and we look forward to being able to take account of the outputs from the European Commission consultation and advisory process. EASAC has previously noted that the scientific community has a responsibility to help EU regulators understand the changing boundaries of synthetic biology. In our view it is important that synthetic biology is covered in the already available legislation and risk assessment that is embedded within the current procedures for GMOs and biotechnology more broadly, rather than conceiving new, separate legislation focusing only on synthetic biology. Thus, 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.	

20	Fears Robin, European Academies Science Advisory Council, RobinFears@aol.com, United Kingdom	3.3.2 Regulatory aspects (GMO-regulation, Convention on Biodiversity)	CONTINUED..... The main conclusions emerging from these statements and recommendations are, section 3.3.2.3; p.19, l.9 onwards As this text is based on the analysis of conclusions emerging from previous work, including that by EASAC, we wish to emphasise one particularly relevant issue. In our EASAC work on GM-crops (cited p.17, l.38), we referred to the reservations often expressed about an overly stringent application of the precautionary principle, given the inevitable uncertainty relating to any new technology. In our view, the use of the precautionary principle to provide an EU context on the risk of innovation must also take into account the risk of not doing research and supporting innovation in the face of considerable societal needs globally (in health, agriculture and the environment for instance). It is also essential for the EU to take account of accumulating evidence base collected outside the EU. Thus, we agree that the present consultation is focusing on a key point relating to the use of the precautionary principle, when it asks (p.19, l.7), "How will it be possible to address this concept for SynBio applications?" This issue is an important one for further consultation on benefit-risk assessment. Regulatory aspects in the United States, section 3.3.2.4; p.21, l.1 onwards It is worth observing that a more recent analysis updates and extends this analysis, concluding that "US regulatory agencies have adequate legal authority to address most, but not all, potential environmental, health and safety concerns posed…synthetic biology" (for further details, including the exceptions, see http://www.jcvi.org/cms/fileadmin/site/research/projects/synthetic-biology-and-the-US-regulatory-system/full-report.pdf). Views and initiatives at the international level, section 3.3.2.8;	Policy decisions are outside the scope of the SCs. The SCs can only reflect on uncertainties in the assessment of risks of SynBio and will do so in Opinion II. SCs have now made reference to this publication in section 3.3.2.8 on other regulations, guidelines and recommendations.

			p.23, l.24 onwards We agree that there is need for a common approach to regulation internationally. Recently, IAP-the global network of science academies published a statement on synthetic biology drawing on both previous activities by science academies and new expert discussion globally (http://www.interacademies.net/10878/Scientific_Opportunities_and_Good_Governance.aspx). The IAP statement recommends greater clarity in definition and in explaining what, if anything, is different from the genetic engineering technologies already in widespread use. The IAP statement also addresses some of the issues raised by the recent work of the Convention on Biological Diversity (section 3.3.2.9) and notes the importance of (i) questioning the underlying assumption that some methodologies are unregulated and (ii) ensuring the use of robust, peer-reviewed evidence when developing policy options. The IAP statement also covers issues for: preparing researchers for work in synthetic biology; engaging with the public; considering alternative models for owning and sharing data; determining how synthetic biology should be regulated; and disseminating guidelines on scientific responsibility. Some of these issues are also highlighted in the recent article by Professor Volker ter Meulen, co-chair of IAP in the Nature special issue cited previously. At the international level, it is also important to take account of the recent work of OECD, published in 2014 (http://dx.doi.org/10.1787/9789264208421-en).	

21	Fears Robin, European Academies Science Advisory Council, RobinFears@aol.com, United Kingdom	3.3.2 Regulatory aspects (GMO-regulation, Convention on Biodiversity)	CONTINUED…… Other regulations, guidelines…., section 3.3.2.10; p.25, l.12 onwards We wish to emphasise the critically important role of the scientific community in encouraging and ensuring responsible research conduct. This responsibility in synthetic biology is highlighted in the IAP 2014 statement and elaborated more generally in previous IAP-IAC work (see http://www.interacademies.net/10878/19787.aspx). It is necessary that all the research community, including Do-It-Yourself (DIY) researchers engages in the development and implementation of appropriate codes of conduct. Without the responsible actions of individual researchers and their institutions, formal regulatory frameworks cannot be effective. The European Commission, in turn, has a responsibility to support the relevant infrastructure and training in support of responsible research. Scope and definition, section 3.3.3.1, p.27, l.7 onwards The proposed scope is consistent with the points made previously in our response that synthetic biology should be considered within the broader context of biotechnology and related sciences, and not separately. The inclusion and exclusion criteria seem well thought out and are able to be set into an operational context. When considering the broader context for inclusion, it is important to remember, as discussed in detail in the EASAC report of 2010, that as well as the regulations appertaining to research governance the EU also has sector-specific mechanisms to control the approval of any novel products emanating from synthetic biology applications (consultation Annex IV, p.55, l.1 onwards). These sector-specific products should generally be subject to the same regulatory framework as exists for other products in that sector derived from other sources.	See above.

22	Grimm Frauke, Federal Agency of Nature Conservation (Bundesamt für Naturschutz, BfN), GrimmF@bfn.de, Germany	3.3.2 Regulatory aspects (GMO-regulation, Convention on Biodiversity)	This chapter should be reworked for more clarity and better structure (e.g. first mention what relevant regulations are in place, what they signify and then how they may or may not apply to SynBio organisms; lengthy historical discourses or current discussions are not that relevant). Page 17, line 15 ff.: This example gives the subject NPBT too much weight considering it is not subject of this opinion. The uncertainties concerning GMO definition and NPBT and their potential consequences on research and development should be mentioned in text in one or two sentences. Page 18, line 21 ff.: Are not the commonly identified questions concerning SynBio also conclusions of the official statements? They should be mentioned in chapter 3.3.2.3. Furthermore, the conclusions listed in 3.3.2.3 should be put into context of these identified questions. Page 19, line 19 ff.: The comparative approach is mentioned without relating it to synthetic biology and the potentially problematic absence of a suitable comparator. Page 20, line 3 ff.: It is mentioned that some SynBio products may or may not be covered by existing legislation. Surprisingly, in the given example protocells and non-canonical information carriers are categorized as living organisms. This is debatable and should be put more clearly in the text, perhaps by adding: “may be considered living organisms under certain conditions”. Page 20, line 10 ff.: Are line 20 ff. still part of the main conclusions taken from official statements on SynBio in Europe? They do not sound as such. Page 23, line 22 ff.: Isn’t it more noteworthy that Brazil authorized commercial release of GM mosquitoes? And	Thank you for your suggestion. The text has been modified as follows: Page 16: Deletion of lines 1-12 of page 16 : it only reflects the historical background against which the EU GMO regulatory framework has been developed Deletion of lines 16-23: only illustrates line 14-15. Deletion of lines 33-36: "This regulation…agriculture and environment”: only reflects the historical background. Page 17: Deletion of lines 5-6 : “this pertains to the current regulatory …the legal status’ Line 9-39: the text of the textbox was partly merged with the main text (to avoid overlaps) while other parts of the textbox were added as a footnote, thereby reducing the weight given to NPBT. Points A to D on p. 19 summarise the conclusions that have been put forward by different institutes and governmental organisations as a response to commonly identified questions. Therefore 3.3.2.2 and 3.3.2.3 were merged into one in the adapted version. The key message here is that it remains unclear whether key principles underlying GMO regulatory framework would still work for SynBio. These key principles are briefly explained in the context of GMO. Analysis on whether and how these key principles could be applied for SynBio is not the scope of this chapter, nor of this Opinion.

			besides, is this information relevant (it's debatable if the GM mosquitoes were produced using synthetic biology or classic biotechnology methods)? Page 23, line 33 ff.: The Cartagena Protocol on Biosafety should at least be mentioned once before it is abbreviated.	Point is well taken. See adapted version: "Synbio systems such as protocells are not (yet) considered as living organisms. On the contrary, xeno nucleic acids/orthogonal systems of hereditary material may be considered as nucleic acids, as mentioned in the GMO regulation". Although protocells (just like "naked" DNA molecules) are *per se* not alive, the potential of protocells as precursors to fully synthetic cells and its deployment to modify the capabilities of living organisms clearly qualify them as part of synthetic biology research. See also p. 15, line 45. Point is well taken. Proposal: start line 10 with 'The SC also notes that….' (see adapted version) The purpose of lines 22 and 23 was to illustrate an experience of GMO management and authorization processes only. The inclusion of this example is not mandatory and it can simply be removed. See the adapted version. Thank you for your comment.
23	Van der Vlugt Cecile, National Institute for Public Health and the Environment (RIVM), cecile.van.der.vlugt@rivm.nl, Netherlands	3.3.2 Regulatory aspects (GMO-regulation, Convention on Biodiversity)	This is an elaborated paragraph on regulatory aspects in EU, statements on SynBio, conclusions and further regulatory aspects outside the EU. This paragraph asks a lot of attention, and interrupts the thoughts on the formulation of the definition. Actually, the only important aspect is whether there is a definition of synthetic biology in other countries outside the EU and if yes, if there is specific regulation. We therefore prefer to shorten the text by e.g. using a Table or Annex to present regulatory issues per country (3.3.2.4 – 3.3.2.10) and include conclusions in the main text (e.g. only the VS has adopted regulations on synbio). We propose to omit paragraph 3.3.2.1, since this paragraph will be more useful in opinion 2 on risk assessment. Furthermore, we suggest to include a	Thank you for your comment. The proposed version of Chapter 3.3.2 has been shortened and reworked. SCs think that focus of the opinion should not be restricted to the set-up of a definition or specific regulation. For the purpose of this Opinion, we considered relevant existing regulatory frameworks for SynBio and initiatives that could give answers to the question whether the set-up of a specific regulatory regime for SynBio would be necessary. See adapted version. Historical background has been removed and the weight given to some parts of the

			shortened version of paragraph 3.3.2.2 and 3.3.2.3.	text has been reconsidered.
24	Van der Vlugt Cecile, National Institute for Public Health and the Environment (RIVM), cecile.van.der.vlugt@rivm.nl, Netherlands	3.3.2 Regulatory aspects (GMO-regulation, Convention on Biodiversity)	3.3.2.3, page 20 We interpret the text in section 3.3.2.3. - elements A to D - as a general summary of the information referred to. It is however not clear whether the text following section D (lines 10 through 43 on page 20) reflects the opinion of the SCENIHR or should be read as a summary text as well. Please explain.	Thank you for your comment. SCs have clarified this point in the adapted version.
25	Boyce Andy, BBSRC (on behalf of the UK Research Councils), andy.boyce@bbsrc.ac.uk, United Kingdom	3.3.2 Regulatory aspects (GMO-regulation, Convention on Biodiversity)	Comment on page 17 line 40: ERASynBio Strategic Vision missing from this list. The ERASynBio Strategic Vision was produced through 18 months of policy work by 16 funding and policy and funding organisations in Europe and the US. It is based on a comprehensive analysis of the field and contains a detailed agreed vision for the field as well as a series of targeted recommendations. The vision exceeds your 1MB upload limit, but it is available at: https://www.erasynbio.eu/lw_resource/datapool/_items/item_58/erasynbiostrategicvision.pdf Comment on page 19 line 8: Although the precautionary principle is an important scientific risk management, its application has been negative for GM research. There are lessons to be learned for how this can be more successfully applied to SynBio. Comment on page 19 lines 17 - 19: Assessment of each GMO independently is considered by many as a very negative aspect of the GMO regulation which has damaged European research and industry. There is a drive from several member states to regulate the product rather than the organism or process. If new regulations are being considered then the GMO regulation should not be de-facto starting point.	The SCs agree. ERASynBio has been included in the text Section 33.1 and 3.3.2.2. This is a point of view, not a remark on how to improve the text of our Opinion. Policy decisions on how the precautionary principle should be applied go beyond the scope of work of the SCs SynBio. This is a critical point, but this decision is made by the politicians, not by the SCs as part of the risk assessment community. This comment is outside the scope of the mandate of the SCs. The key message in our Opinion is that it remains unclear whether key principles underlying GMO regulatory framework would still apply for Synbio. These key principles are briefly explained in the context of GMO. Whether or not these key principles could be applied for Synbio is not the scope of this Chapter, nor of this first Opinion. This analysis will be developed in Opinion II. This is a point of view, but outside the scope of the mandate of the SCs.

			Comment on lines page 22 lines 7 - 8: This would be a much appreciated model for EU SynBio regulation which, as noted, as proves effective in countries including Canada.	
26	Edmundson Matthew, University of Edinburgh, medmunds@staffmail.ed.ac.uk, United Kingdom	3.3.2 Regulatory aspects (GMO-regulation, Convention on Biodiversity)	Page 22, lines 4-16 The regulatory example from Canada would seem like a good starting point for regulating SynBio; the products and techniques of SynBio are the potentially hazardous aspects of SynBio rather than the concept of SynBio itself.	This is a point of view, but outside the scope of the mandate of the SCs.
27	Grimm Frauke, Federal Agency of Nature Conservation (Bundesamt für Naturschutz, BfN), GrimmF@bfn.de, Germany	3.3.3 Elements of a definition (based on inventory)	Page 27, line 19 ff.: The rationale for the exclusion criterion should be given, especially as some biological entities produced via SynBio are thus exempted from this definition and all following considerations on e.g. risk assessment. Page 27, line 26 ff.: The reason for adding “to alter living or non-living materials” to the definition of SynBio is not clear. Please explain why this addition was necessary.	This remark probably is again about pre-life stages of protocell and bionanoscience work. This needs to be clarified indeed (see comments 9 and 17 above). The SCs should clarify that protocells and bionanotech fall under the domain of nanotechnology and chemistry respectively, as long as they are not being used to produce living organisms. They are, however, important in the preparatory work of SynBio and contribute to the long-term aims of SynBio research. Although protocells (just like “naked” DNA molecules) are *per se* not alive, the potential of protocells as precursors to fully synthetic cells and their deployment to modify the capabilities of living organisms clearly qualify them as part of synthetic biology research. The text on protocells in section 3.3.1.3 was amended accordingly. The SCs agrees and removed this phrase. One could envisage uses of SynBio that do not alter materials of any kind.

28	Van der Vlugt Cecile, National Institute for Public Health and the Environment (RIVM), cecile.van.der.vlugt@rivm.nl, Netherlands	3.3.3 Elements of a definition (based on inventory)	3.3.3.1, page 25, line 26-31 This alinea refers to the thought that synbio is an extension of genetic modification and the definition of a GMO seems to be an important stepping stone for the proposed definition. If so, this should be stated more clearly in the opinion. It could also be helpful for the reader to indicate that synbio relating to genetic modification is framed as a starting point for opinion 2 and 3, and that other areas of synbio are currently regarded as chemistry.	SCs agree that this thought should be clearly expressed in this section, but also believes that this has been done: see in particular paragraph 6 and the last paragraph in this section. Nevertheless one additional introductory sentence has been added in this first paragraph of section 3.3.3.1.
29	Van der Vlugt Cecile, National Institute for Public Health and the Environment (RIVM), cecile.van.der.vlugt@rivm.nl, Netherlands	3.3.3 Elements of a definition (based on inventory)	3.3.3.1, page 26, line 1 'of practical value', what is meant here? Is 'practical' referring to a definition for synbio in which the research areas of synbio related to genetic modification are framed? And is this framing meant for considering those areas which should be subject to a (environmental) risk assessment? Is it legitimate to exclude the other research areas of synbio in this way? Please note, we understand and agree upon these choices, but we ask to be more explicitly on these choices.	SCs agree with this request for more clarity and now explain that this framing is for the purpose of risk assessment.
30	Van der Vlugt Cecile, National Institute for Public Health and the Environment (RIVM), cecile.van.der.vlugt@rivm.nl, Netherlands	3.3.3 Elements of a definition (based on inventory)	3.3.3.1, p. 27 line 1-28 and p. 28 line 1-12. We miss the rationale for the current definition, inclusion and exclusion criteria. The definition and criteria seems to be a slightly extended GMO definition. Although we understand this approach, please explain the rationale to come to this definition in the context of synbio by discussing the elements of the definition and the rationale for the inclusion and exclusion criteria.	Based on this and similar comments as well the minority opinion in the Preliminary Opinion, the SCs discussed this point and decided to be more transparent about the reasoning behind the definition and the inclusion and exclusion criteria. This reasoning is now elaborated at the end of this section.
31	Van der Vlugt Cecile, National Institute for Public Health and the Environment (RIVM), cecile.van.der.vlugt@rivm.nl, Netherlands	3.3.3 Elements of a definition (based on inventory)	page 27, line 19-22 What is the rationale to exclude work on biological entities that are not capable of replication or of transferring genetic material? Why is this work not part of synbio?	The SCs should clarify that protocells and bionanotech are in the domain of nanotechnology and chemistry as long as they don't produce living organisms. They are important preparatory work, contributing to the long-term aims of SynBio research. Although protocells (just like "naked" DNA molecules) are *per se* not alive, the potential of protocells as precursors to fully

				synthetic cells and their deployment to modify the capabilities of living organisms clearly qualify them as part of synthetic biology research. The text on protocells in section 3.3.1.3 was amended accordingly.
32	Van der Vlugt Cecile, National Institute for Public Health and the Environment (RIVM), cecile.van.der.vlugt@rivm.nl, Netherlands	3.3.3 Elements of a definition (based on inventory)	page 27, line 26-28 What is meant by 'non-living materials' in the proposed definition?	Something that doesn't live, but is modified/acted on by something that does. This is defined in footnote 31. However, SCs decided to drop this phrase from the definition (see comment 27).
33	Gent Ricardo, German Association of Biotechnology Industries (Deutsche Industrievereinigung Biotechnologie), gent@dib.org, Germany	3.3.3 Elements of a definition (based on inventory)	p. 27, lines 26-28: The definition of synthetic biology proposed in the document is not operational since it lacks discrete scientific criteria that would qualify a certain research activity as synthetic biology. According to such a definition, many techniques that have been in use over the past several decades in the EU could be construed as synthetic biology. The proposed definition is also unsuitable to address regulatory provisions, because it is based on the techniques used to develop synthetic biology products and not on the resulting products themselves. To accurately and appropriately address the next two mandated Opinions (risk assessment methodology, safety aspects and research priorities), the analysis must be based on the characteristics of the product which determines its safety, not the techniques which led to the product and which in themselves do not pose a specific safety hazard. DIB suggests that the European Commission makes the definition of synthetic biology specific and fully viable. In our view, the current proposal is not sufficient to preserve legal certainty. An approach in line with the Minority Opinion (p 30) at defining Synthetic Biology would provide a more practical, scientific and meaningful start for defining synthetic biology. We recommend further dialogue with practitioners from	The survey of existing definitions of SynBio clearly shows that the definition has to be process-based, not product-based, to be viable. Based on this and on similar comments in the Minority Opinion published within the Preliminary Opinion, the SCs discussed this point and decided to be more transparent about the reasoning behind the definition and the inclusion and exclusion criteria. This reasoning is now elaborated at the end of this section. It also shows more clearly why a product-based definition does not hold.

			industry, academia and society to assist in the development of a clear definition.	
34	Boyce Andy, BBSRC (on behalf of the UK Research Councils), andy.boyce@bbsrc.ac.uk, United Kingdom	3.3.3 Elements of a definition (based on inventory)	Comments on page 26 line 3 - 5: The items that are quoted here (rational design, standardisation, modularity etc.) are the defining features of synthetic biology. You cannot redefine the field because it does not fit with what you are trying to do. Comments on page 26 lines 11 - 12: The engineering concepts described above are not abstract. They are well defined and understood within the engineering community. Their use within synthetic biology is also widely accessible in freely available publications. Comment on page 27 line 7 - 8: This inclusion criteria is very misleading. Genetic modification has been practiced routinely for decades. SynBio is a new approach with a distinctly different approach and scope. This statement implies that all existing and historical GM research fits within the scope of SynBio. Comments on page 27 lines 19 - 22: This exclusion removes a large amount of existing synthetic biology research in the area of protocells (http://www.ruhr-uni-bochum.de/ECCell/) and bionanoscience (http://www.sciencemag.org/content/340/6132/595.full?sid=f422d963-74c5-488e-910e-8ed681eace73)	SCs argue that we are not redefining the field, but chose to define it in an operational way for the purpose of risk assessment in line with the questions of the mandate. Abstract engineering concepts can be well defined and understood. Abstract does not mean unclear. "*Abstraction is a process by which concepts are derived from the usage and classification of literal ("real" or "concrete") concepts, first principles, or other methods."* The working group tried to define the relationship between genetic modification and synthetic biology on the basis of quantifiable and currently measurable inclusion and exclusion criteria. Presently, however, the SCs did not conclude that these criteria meet the requirements of being quantifiable and currently measurable. Based on this and similar comments as well as on the Minority Opinion in the Preliminary Opinion, the SCs discussed this point and decided to be more transparent about the reasoning behind the definition and the inclusion and exclusion criteria. This reasoning is now elaborated at the end of this section. SCs now clarified that protocells and bionanotech are in the domain of nanotechnology and chemistry as long as they don't produce living organisms. They are important in the preparatory work, contributing to the long-term aims of SynBio research, but they are not

				considered part of SynBio (unless we redefine "biology"). The text on protocells in section 3.3.1.3 was amended accordingly and repeated in section 3.3.3.
35	Horsfall Louise, University of Edinburgh, louise.Horsfall@ed.ac.uk, United Kingdom	3.3.3 Elements of a definition (based on inventory)	Lines 26-28 Based on all the evidence and discussion given throughout, including the list of concepts, I reject the proposed science-based working definition. It lacks the required inclusion of engineering principles which are contained in the concept of SynBio. SynBio may 'facilitate and accelerate the design, manufacture and/or modification of genetic materials in living organisms to alter living or non-living materials', but other non-SynBio techniques would also fall under this definition.	SCs think that including engineering principles wouldn't change anything in terms of what is covered by the definition: GM has always used modularity and standards and rational design; there are plenty of examples, and that's why it has been called Genetic Engineering for a long time. On the other hand, adding engineering principles in the definition would make it even less usable: who is going to decide whether someone used engineering or just tinkered around with some genes…?
36	Davies Jamie, University of Edinburgh (but giving a personal opinion, not one ratified by the organization), jamie.davies@ed.ac.uk, United Kingdom	4 OPINION	Why is your definition of synthetic biology focused on 'genetic materials'? A major arm of synthetic biology - the synthesis of 'life' from non-living chemicals - may not use genetic materials at all. Also, even in 'mainstream' synthetic biology (e.g. of mammalian cells), really significant changes can be made by modification of epigenetics. I fear you have been taking opinions from a rather closed group who are very DNA-centred: these narrow opinions may serve you well for the next few years, but in the long-term could prove to be regrettably narrow. There is a simple alternative way to look at this, a way that is directly analogous to the way the word 'synthetic' is used in chemistry. Chemistry is divided into analytical chemistry (study what exists) and synthetic chemistry (make something new). It would be simple to divide biology into analytical biology (the study of existing cells, tissues and organisms) and synthetic biology (the creation of new or modified cells, tissues	For the SCs, genetic material is not the same as DNA. It means any physical carrier of information that is inherited to offspring. All true synthesis of life aims at creating an organism that replicates and passes on genetic information. Our definition contains no bias concerning the source or chemical basis of this genetic material. We have clarified the text for "Genetic material" in section 3.2. The SCs agrees that a long-term vision would define SynBio as the creation of new or modified cells, tissue, organisms. Our definition aims at being more specific in that modifications that are not heritable are excluded.

			and organisms). This will cover all aspects of synthetic biology, and will not tie the definition down to the current obsessions of early 21st-century scientists.	
37	Fears Robin, European Academies Science Advisory Council, RobinFears@aol.com, United Kingdom	4 OPINION	Opinion, section 4; p.28, l.32 onwards We agree that it is challenging to find a succinct and meaningful definition of synthetic biology, with comprehensive yet unambiguous definition of scope. In the recent IAP work, the following introductory text was used, “Synthetic biology is the deliberate design and construction of customised biological and biochemical systems to perform new or improved functions. It draws on a wide range of disciplines and methodologies to design molecules, construct genetic circuits, and assemble simple organisms.” The IAP statement also provides examples of new research advances and potential applications. We favour the majority opinion presented. The minority opinion would require continuing updating and revision of criteria as technologies develop, and would be difficult to use for practical purposes as it includes imprecise terms such as “a significant proportion” (p.31, l.17 and footnote 31), “a part of it” (p.31, l.19) and “a significant proportion (p.31, l.20).	SCs discussed this point again and acknowledge the difficulties in the minority Opinion. The SCs analysed the reasoning behind the minority Opinion and have added a section illustrating the reasoning behind the definition and the inclusion and exclusion criteria. This reasoning is now elaborated at the end of this section.

38	Dr. Zellmer Sebastian, German Federal Institute of Risk Assessment, sebastian.zellmer@bfr.bund.de, Germany	4 OPINION	The suggested definition of synthetic biology seems not precise enough as it misses out on important concepts and applications summarised by this term. As presented the definition does not differentiate between genetic modification of organisms and synthetic biology. While synthetic biology might well comprise the genetic modification of an organism, the concept as such far exceeds molecular cloning of single genes or gene components. Synthetic biology makes use of whole interacting genetic networks and genomes as well as the use of targeted modifications of metabolic pathways and enzymes [1]. Apart from genetic modifications the latter can for example include natural selection and optimised fermentation of unmodified organisms or the production of metabolites and enzymes thereof. Metabolic networks on the other hand are usually first generated in silico, allowing to design and integrate novel pathways [2]. The resulting changes in the metabolism can be simulated. Also, the efficiency of these networks can be simulated and subsequently optimized prior to any genetic modification of an organism. The main strength of synthetic biology is the use of large data bases and bioinformatic tools for generation of organisms, metabolites or proteins together and the simulation and optimisation of the respective features in silico. For example Gibson and co-worker [3] synthesized the DNA of Mycoplasma mycoides and transplanted it into M. mycoides, thereby generating a novel organism. This shows that synthetic biology covers also chemically synthesized DNA. Recently, this approach was extended to the complex genome of yeast [4]. Therefore, artificially designed DNA is part of synthetic biology. Consequently, the definition should include the in silico design and optimization of organisms as well as the targeted use of proteins and growth conditions.	Thank you for your comment. Design of DNA is covered by our definition, as is the production of metabolites or enzymes, and in modified organisms. We argue that using a wild type material and growing it in new conditions would not be SynBio. SCs have revised the Opinion and included the reasoning for why the definition does not differentiate between genetic modification and SynBio. The main challenges in SynBio remain biological. Design is included; it does not matter if that happens in silico or on a whiteboard because these other aspects are not “synthetic”. Thank you. We checked these references. The first one is cited (note 9). The second one is considered not critical for this Opinion. The third one is cited as well. The 4th one is considered very relevant for Opinion 2 and will be used there.

			References: 1. Capurro, R., Kinderlerer, J., DaSilva, P.M., Rosell, P.P., 2010. Opinion of the European Group on Ethics in Sciences and New Technologies to the European Commission: Ethics in synthetic biology. Salvi, M. 25: 1-57. Luxembourg: Luxembourg Publications Office of the European Union. 2. Jouhten, P., 2012. Metabolic modelling in the development of cell factories by synthetic biology. Comput.Struct.Biotechnol J 3: e201210009. 3. Gibson, D.G., Glass, J.I., Lartigue, C., Noskov, V.N., et al., 2010. Creation of a bacterial cell controlled by a chemically synthesized genome. Science 329 (5987): 52-56. 4. Annaluru, N., Muller, H., Mitchell, L.A., Ramalingam, S., et al., 2014. Total synthesis of a functional designer eukaryotic chromosome. Science 344 (6179): 55-58.	
39	Grimm Frauke, Federal Agency of Nature Conservation (Bundesamt für Naturschutz, BfN), GrimmF@bfn.de, Germany	4 OPINION	Page 28, line 19 ff.: Why are the approaches (technologies, methods etc.) to develop GMOs important for responsibly addressing societal challenges? Page 28, line 30: Why does the operational definition need to responsibly address societal challenges in the areas of health, energy and food security? Besides, it does not do this. Page 29, line 16 ff.: The information that current developments in the field of SynBio lead to organisms that fall within the remit of existing regulation is important but out of place in this context. This information should be placed in the answer to question 1. Page 29, line 23 ff.: It was stated before that existing definitions were not suitable as operational definitions, thus it is surprising that existing definitions will potentially contribute	The SCs think this is because we need to assess the risk of new organisms, and for that we need to know how they have been made to have an idea what could go wrong. In view of societal pressure to explain new and emerging risks, the wording was slightly changed and a pertinent reference added. We agree and have changed the sentence to answer question 1. Elements of the definitions will potentially contribute and it is possible even if the definitions themselves are not suitable for our purposes.

			to an operational definition using specific inclusion and exclusion criteria. Could it be that “that” in line 24 was meant to be “and”?	
40	Elbing Kerstin, German Life Science Association (VBIO e. V.), elbing@vbio.de, Germany	4 OPINION	We doubt, that the proposed definition (“SynBio is the application of science, technology and engineering to facilitate and accelerate the design, manufacture and/or modification of genetic materials in living organisms to alter living or non-living materials.”) meets the predefined benchmark to provide an “operational definition of Synthetic Biology“. In our view it lacks discrete, scientific criteria which distinguish Synthetic Biology from conventional gene technology. Therefore in practice it does not allow to distinguish a certain research activity as practicing Synthetic Biology or not. But at least at the point of risk assessment (opinion 2) or defining research priorities (opinion 3), a strict and clear definition is a prerequisite. Moreover: This lack of accuracy might lead to defining research activities as "Synthetic Biology“ which are already regulated by other EU legislation. This kind of double coverage has to be avoided. (see also p. 15 39ff.. Although SynBio is a relatively new field, the existing regulations applicable to biological, chemical or genetic modification research and products are also applicable to SynBio research, applications and products and Annex IV). Our recommendations for further discussion • The definition of Synthetic Biology should be modified to make it more specific and usable. To reach this objective an enhanced further dialogue with practitioners from academia (and industry) is strongly recommended to provide a selective, reliable and thus operable definition for Synthetic Biology. • Definition (and in the long run possibly regulation) should focus on the construction of completely new pathways using	SCs have adapted the Opinion to include the reasoning behind the definition and inclusion and exclusion criteria, which is elaborated at the end of section 3.3.3 This will be a continuous process. A more specific definition may result in early obsolescence. Therefore, we defined SynBio in broad terms. The present definition allows for the rapidly advancing nature of GM technologies and important nuance that supports the need for on-going updates of risk assessment methods, which will be addressed in Opinion II.

			multiple genes from different species or de novo synthesis of living entities. • Whatever definition will be the outcome: All activities, which fall under this definition but are already regulated by other EU Regulations need no special regulation under the head “Synthetic Biology”. In particular organisms or natural products that are generated by gene technology need not to be covered and vice versa. In case emerging tools of gene technology challenge the existing regulations of gene technology the latter ones might be adapted within its separate rationale. German Life Science Association will follow the ongoing process of definition, risk assessment and research priorities in the field of synthetic Biology. We are willing to bring in the expertise of our members and member societies.	
41	Strassheim Swantje, German Federal Office of Consumer Protection and Food Safety, Department Genetic Engineering, swantje.strassheim@bvl.bund.de, Germany	4 OPINION	The final definition given by the SC is the following: SynBio is the application of science, technology and engineering to facilitate and accelerate the design, manufacture and/or modification of genetic materials in living organisms to alter living or non-living materials. To my mind, this definition does not include the research approaches on protocells that try to establish a “chassis” from chemical parts. For example, an artificial vesicle made of fatty acids able of RNA replication (Adamala and Szostak 2013) is not comprised in the “design, manufacture and/or modification of genetic materials in living organisms” as this kind of protocell would only become a living organism when RNA replication actually occurs. Therefore, the design and manufacture of vesicles that grow and/or self-replicate, which is also part of protocell research, would not be covered by the	See the answer to comments no. 9, 17, 22, 27, 31. Protocells is a route towards achieving true SynBio. Like DNA synthesis is. Living organisms (as defined by Cartagena etc.) will always contain genetic material and their design or manufacture will also involve the design/manufacture/modification of this genetic material, so the case described in the extended discussion is actually covered by the more concise version in the Opinion. The SCs should clarify that protocells or bionanotech are in the domain of nanotechnology or chemistry as long as they don’t produce living organisms. They are important preparatory work, contributing to the long-term aims of SynBio research, Although protocells (just like “naked” DNA molecules) are per se not alive, the potential of protocells as precursors to fully synthetic cells and its deployment to modify the capabilities of

			definition. I would thus suggest adding the following (addition underlined): SynBio is the application of science, technology and engineering to facilitate and accelerate the design, manufacture and/or modification of genetic materials in living organisms or the design or manufacture of living organisms themselves to alter living or non-living materials. That way, the definition would also cover the design, manufacture and/or modification of living organisms as attempted e.g. by Adamala and Szostak.	living organisms clearly qualify them as part of synthetic biology research. The text on protocells in section 3.3.1.3 was amended accordingly The reference is included in Opinion II; it was not considered relevant for Opinion I.
42	Dr. Brandt Stephan, Federal Ministry for Health, Germany, 115@bmg.bund.de, Germany	4 OPINION		SCs thank you for the comment. The phrase “biological entities” cannot replace “genetic materials in living organisms”, because it broadens the scope of the definition. To address this comment, we provided a more detailed section on the reasoning behind the definition and the inclusion and exclusion criteria. This reasoning is now elaborated at the end of section 3.3.3. With regard to work on protocells: see our previous answer to comments no. 9, 17, 22, 27, 31, 41.

43	Mensik Petr, Federation of European Specialty Food Ingredients Industries (ELC), elc@ecco-eu.com, Belgium	4 OPINION	ELC, the Federation of European Specialty Food Ingredients Industries, would like to thank the European Commission and its Scientific Committees for the opportunity to submit comments on the first preliminary opinion on Synthetic Biology –Definition. The ELC believes that the objective of creating a working definition for synthetic biology should be to identify novel applications that are outside the current realm of genetic engineering that could require additional regulatory assessment. Because effective GM regulations exist in the European Union as well as in many parts of the world, a significant number of the products that would be included in the proposed definition are already well-regulated and safety assessed. The Minority Opinion expressed on page 31 of the document begins to meet the objective of differentiating applications of synthetic biology from applications of genetic engineering. In particular, the two elements below are helpful in making the distinction: • Modular genetic parts have been utilized to rationally (re)design and assemble a new or altered biological function • A genetic construct in its composition contains artificial (unnatural) nucleotides However, the Minority Opinion does not clearly enough differentiate synthetic biology from genetic engineering for it to be useable. We would respectfully recommend further dialogue with practitioners from industry and academia to assist in development of a clearer definition.	SCs thank you for the comment. To address this comment, we provided a more detailed section on the reasoning behind the definition and the inclusion and exclusion criteria. This reasoning is now elaborated at the end of section 3.3.3.
44	Boyce Andy, BBSRC (on behalf of the UK Research Councils), andy.boyce@bbsrc.ac.uk,	4 OPINION	Comment on page 28 lines 25 - 27: The reason that most definitions emphasise this is because these engineering concepts are the defining feature of synthetic biology. You cannot redefine the field because it does	The SCs are providing a definition of what is actually happening, rather than a conceptual vision that is useful for academic science, but irrelevant in practice, especially when it addressing risk assessment and

	United Kingdom		not fit with what you are trying to do. Comment on page 29 line 1 - 2: This is very misleading. Genetic modification has been practiced routinely for decades. SynBio is a new approach with a distinctly different approach and scope. This statement implies that all existing and historical GM research fits within the scope of SynBio.	regulations. To address this comment, we provided a more detailed section on the reasoning behind the definition and the inclusion and exclusion criteria and how GM and SynBio differ. This reasoning is now elaborated at the end of section 3.3.3.
45	Edmundson Matthew, University of Edinburgh, medmunds@staffmail.ed.ac.uk, United Kingdom	4 OPINION	Page 28, lines 25-34 This section states that most definitions of SynBio make reference to modularity and other engineering concepts contained in SynBio. However it goes on to say that this is not sufficient for an 'operational definition' and omits these important concepts from the proposed definition. Page 28, lines 32-34 The proposed definition seems to state that SynBio is synonymous with GM. While SynBio utilises many GM techniques it is not itself 'GM'. As stated in the comment above the proposed definition also does not cover the important engineering principles contained in the concept of SynBio. SynBio does 'facilitate and accelerate the design, manufacture and/or modification of genetic materials in living organisms to alter living or non-living materials', but other GM techniques also can also accomplish this by other means. SynBio specifically achieves these aims by utilising the principles of standardisation and engineering, using GM tools in a novel manner.	To address this comment, we provided a more detailed section on the reasoning behind the definition and the inclusion and exclusion criteria. This reasoning is now elaborated at the end of section 3.3.3.
46	Cannell Martin, Defra, martin.cannell@defra.gsi.gov.uk, United Kingdom	4 OPINION	The mainstream definition in this report recognises that, whilst it is useful to seek some form of consensus regarding the meaning of 'synthetic biology', identifying a clear separation between genetic modification and synthetic biology is currently not a practical prospect. The report correctly highlights that	Thank you. This adequately summarises our Opinion.

			with regard to the organisms produced using techniques of synthetic biology, these will generally be GMOs and adequately regulated as such ensuring safety to human health and the environment. However, as some aspects of synthetic biology develop and progress, some organisms and products may increasingly challenge the regulations and existing approaches to risk assessment – especially where the intention is to release organisms into the environment. The regulations governing contained uses of GMOs are less likely to be challenged in the same way.	
47	Grimm Frauke, Federal Agency of Nature Conservation (Bundesamt für Naturschutz, BfN), GrimmF@bfn.de, Germany	5 MINORITY OPINION	Sensible points are brought up in the minority opinion. They should be reconsidered, especially line 15 ff. and line 35 ff.	To address this comment and the minority Opinion, we provided a more detailed section on the reasoning behind the definition and the inclusion and exclusion criteria. This reasoning is now elaborated at the end of section 3.3.3.
48	Van der Vlugt Cecile, National Institute for Public Health and the Environment (RIVM), cecile.van.der.vlugt@rivm.nl, Netherlands	5 MINORITY OPINION	page 31, line 12-27 This alternative definition is proposed to distinguish synthetic biology from genetic modification. Although this seems to be a logical approach, the proposed criteria do not distinguish synthetic biology from genetic modification. For example: - chemically synthesized genetic material has already been used for many years in e.g. PCR; - chemically synthesized and 'natural' genetic material are identical; there is, as a matter of principle, no chemical analytical tool possible to detect a difference; as such incorporating 'chemically synthesized' into the criteria has no practical added value; - codon-optimization of a gene is an example of artificial design; - modular genetic parts like promoters and terminators are swopped in all kind of gene constructs. It is just in a name to refer now to modular parts; - genetic circuits have been introduced already for many years,	Thank you for your comment. To address this comment, we provided a more detailed section on the reasoning behind the definition and the inclusion and exclusion criteria. This reasoning is now elaborated at the end of section 3.3.3.

			e.g. IPTG-LacZ operon. Therefore the proposed definition and criteria are not very helpful in framing synthetic biology.	
49	Strassheim Swantje, German Federal Office of Consumer Protection and Food Safety, Department Genetic Engineering, swantje.strassheim@bvl.bund.de, Germany	5 MINORITY OPINION	The Scientific Committees (SC) were asked to answer the question as to what is Synthetic Biology and what is its relationship to the genetic modification of organisms. The SC refer to SynBio as the "progress towards the development of concepts and tools allowing for faster and easier design and manufacturing of GMOs" and concludes that a clear separation between genetic modification (GM) and SynBio is currently not a practical prospect. As stated in the minority opinion given by the SCCS, this regards SynBio equal to GM, which makes it difficult to identify a SynBio product or application for SynBio risk assessment. In GM risk assessment, GMOs are compared to known and characterised reference organisms in order to assess their potential risks. However, SynBio research approaches such as protocells, genome synthesis or xenobiology could lead to organisms that would no longer be comparable to any known and characterised reference organism and therefore would be difficult to assess with the GM risk assessment methodology currently used. For the identification of SynBio products/applications and potential new risk assessment methodologies, it would thus be helpful to make the definition given in the opinion more specific to SynBio. The definition proposed in the minority opinion by the SCCS would therefore be more appropriate to clearly identify SynBio	To address this comment, we provided a more detailed section on the reasoning behind the definition and the inclusion and exclusion criteria. This reasoning is now elaborated at the end of section 3.3.3. The present definition allows for the rapidly advancing nature of GM technologies and important nuance that supports the need for on-going updates of risk assessment methods, which will be addressed in Opinion II. It is noted that the current EU regulatory regime for GMO is not triggered by the applicability (or not) of a certain a risk assessment methodology, it is triggered by the applicability of a definition and the utilization of certain techniques of modification.

			products or applications.	
50	Dr. Brandt Stephan, Federal Ministry for Health, Germany, 115@bmg.bund.de, Germany	5 MINORITY OPINION		See the answer from the SCs to comment no. 42.
51	Boyce Andy, BBSRC, andy.boyce@bbsrc.ac.uk, United Kingdom	5 MINORITY OPINION	Comment on page 30 lines 10 - 39: We strongly agree with the minority opinion expressed here and recommend that it should be taken into account in the final definition. Comments on page 31 lines 12 - 27: This definition addresses some of the concerns with the existing working definition; however it still fails to address the defining feature of synthetic biology - the use of engineering principles. Without this inclusion, no definition will actually capture what synthetic biology is and therefore risks not addressing the areas of concern or impacting on non-synthetic biology activities.	To address this comment, we provided a more detailed section on the reasoning behind the definition and the inclusion and exclusion criteria. This reasoning is now elaborated at the end of section 3.3.3. Engineering was already part of GM; the term emerged in the late 1970s.

52	Edmundson Matthew, University of Edinburgh, medmunds@staffmail.ed.ac.uk, United Kingdom	5 MINORITY OPINION	Page 31, line 1 to page 32, line 28 I concur with the minority opinion in that the proposed definition is very close to that of GM in general. However I also believe that the proposed minority definition is too broad. For example a 'significant proportion of the… genetic material' being 'chemically synthesised' does not necessarily imply the utilisation of SynBio; the genetic material in question could simply be a single gene cloned into a bacterial expression strain and which has been codon-optimised for that strain, i.e. it is not a new 'modular' component and is simply a manifestation of a classical GM technique.	To address this comment, we provided a more detailed section on the reasoning behind the definition and the inclusion and exclusion criteria. This reasoning is now elaborated at the end of section 3.3.3. The observed shortcomings in both the Preliminary Opinion and the Minority Opinion have been addressed.
53	Horsfall Louise, University of Edinburgh, Louise.Horsfall@ed.ac.uk, United Kingdom	5 MINORITY OPINION	Page 31, line 17 Significant needs to be quantified to alleviate uncertainty.	There is always disagreement about exact wording but we do our utmost to use clear and accurate terms. For further explanation, please see the additions to section 3.3.3.
54	Horsfall Louise, University of Edinburgh, Louise.Horsfall@ed.ac.uk, United Kingdom	5 MINORITY OPINION	The 'Minority Opinion' detailed in this report is far more informed and demonstrates a far better understanding of the field than the general/consensus opinion detailed elsewhere.	See our explanations added to section 3.3.3.
55	Geertsma Robert, New & Emerging Technologies SCS [installed by EC DG SANCO Medical Devices Unit], Robert.Geertsma@rivm.nl, Netherlands	8.4 ANNEX IV: Regulatory framework that would apply to the various synthetic biology applications	On page 56, in Lines 21-26, the regulatory framework for medical devices is provided. There is, however, one omission. The third directive of the framework, covering the in vitro diagnostic medical devices, is not listed. Synthetic Biology certainly has (potential) applications in this type of medical devices. The reference is: Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices. OJ L331, 7.12.1998, p1.	Thank you for your comment. This has now been added.
56	Nevoigt Elke, Jacobs University Bremen, e.nevoigt@jacobs-	ABSTRACT	Page 5, line 20-22 SynBio is the application of science, technology and	Thank you for your comments. The SCs note that the two definitions are not identical, and the differences are important: SynBio accelerates and facilitates the

	university.de, Germany		engineering to facilitate and accelerate the design, manufacture and/or modification of genetic materials in living organisms to alter living or non-living materials. My comment: The Definition given for SynBio is virtually the same as the one for BIOTECHNOLOGY given by OECD (see below). Biotechnology is much broader than SynBio since it also applies non-modified biological components such as cells and enzymes, all molecules naturally produced by them and all useful activities delivered by them. In my opinion, the Biotechnology definition already includes SynBio. I strongly suggest defining SynBio as a novel Approach/vision to modify biological systems. This approach can be used within a broad range of applications, i.e. in all traditional fields of Biotechnology and might even create new fields. http://stats.oecd.org/glossary/detail.asp?ID=219 Biotechnology is defined as the application of science and technology to living organisms as well as parts, products and models thereof, to alter living or non-living materials for the production of knowledge, goods and services.	process; we are neutral about how this is achieved, because our definition should not be unduly biased by the preoccupations of early-21st century researchers, but our text outside the definition discusses many recent developments, both conceptually and technologically that contribute to this acceleration and facilitation. Regarding the differences in scope between SynBio and BioTech, both definitions are necessarily very broad when it comes to potential uses and applications – any narrow focus on current or imminent applications would be wrong. We also need to avoid SynBio as a "vision" if we want to have a practically useful definition and avoid subjectivity and loopholes.
57	Grimm Frauke, Federal Agency for Nature Conservation (Bundesamt für Naturschutz, BfN), GrimmF@bfn.de, Germany	ABSTRACT	Page 5, Line 20 ff.: The proposed operational definition of synthetic biology should not be fixed until the conclusion of all three planned scientific opinions on synthetic biology, as it should be possible to test the proposed definition in its suitability and, if necessary, to adjust it. This definition does not encompass, for example, artificial (proto-) cells that are unable to replicate but can influence their environment and other life forms (not necessarily their genetic information) (see e.g. Lentini et al., 2014). It should be mentioned in this abstract, that the incapability of	Thank you for your comment. While the SCs acknowledge the dynamic nature of this field, it was required to present an operational definition. The SCs is well aware that this definition will evolve over time. Thank you for this reference. The SCs now clarified that protocells are in the domain of chemistry as long as they don't produce living organisms. They are important the preparatory work, contributing to the long-term aims of SynBio research, but they are not considered part of SynBio (unless we redefine "biology"). The text on protocells in section 3.3.1.3

			replication is an exclusion criteria (cf. chapter 3.3.3.1). Lentini, R., et al. (2014). Integrating artificial with natural cells to translate chemical messages that direct E. coli behaviour. Nature Communications. DOI: 10.1038/ncomms5012	was amended accordingly and repeated in section 3.3.3.
58	Grimm Frauke, Federal Agency for Nature Conservation (Bundesamt für Naturschutz, BfN), GrimmF@bfn.de, Germany	ABSTRACT	Page 5, line 31 ff.: Synthetic biology is not clearly differentiable from genetic modification of organisms. Nevertheless, synthetic biology could lead to the production of organisms or protocells that may not fall under the regulatory definition of GMO. This difficulty and its consequences should be clearly stated and kept in mind.	The SCs agree. The text on protocells in section 3.3.1.3 and 3.3.3 was amended.
59	Van der Vlugt Cecile, National Institute for Public Health and the Environment, cecile.van.der.vlugt@rivm.nl, Netherlands	ABSTRACT	line 20 The definition proposed by SCENIHR relies heavily on the term 'genetic'. The opinion of the SCENIHR however does not address the interpretation or definition of the term 'genetic'. 'Genetic' can e.g. stand for the coding system (the specific type of chemicals used, but also the coding systematics itself) contained in 'natural' DNA as we currently know it. However, 'genetic' may also refer to the more general concept of the coding of information and processes by chemical means in a more general sense. We ask the Working Group to explain the use of the word 'genetic' and the concepts contained in it.	Thank you for your comment. SCs agree that we need to clarify "genetic" as inheritable material in the wider sense. For the SCs, genetic material is not the same as DNA. It means any physical carrier of information that is inherited by the offspring. All true synthesis of life aims at creating an organism that replicates and passes on genetic information. Our definition contains no bias concerning the source or chemical basis of this genetic material. The term "Genetic material" is now clarified in section 3.2.

60	Gent Ricardo, German Association of Biotechnology Industries (Deutsche Industrievereinigung Biotechnologie), gent@dib.org, Germany	ABSTRACT	p. 5, lines 20-22: The definition of synthetic biology proposed is not operational since it lacks discrete scientific criteria that would qualify a certain research activity as synthetic biology. According to such a definition, many techniques that have been in use over the past several decades in the EU could be construed as synthetic biology. DIB shares the view of the German Research Foundation (DFG) that "The term synthetic biology covers a research and application field that cannot be strictly differentiated from conventional genetic engineering and biotechnological processes. It can therefore be regarded as a further development of these disciplines and their respective objectives." (Source: www.dfg.de/download/.../stellungnahme_synthetische_biologie.pdf)	Thank you for your comment. See our explanations added to section 3.3.3. SCs agree.
61	Boyce Andy, BBSRC (on behalf of the UK Research Councils), andy.boyce@bbsrc.ac.uk, United Kingdom	ABSTRACT	Comment on lines 20 - 22: This is a very limited definition of SynBio that does not fit with currently agreed definitions or the state of the field. Specifically, it limits synthetic biology to the modification of genetic material and ignores the defining feature of synthetic biology, namely the use of engineering principles. Comment on lines 31 - 32: This is very misleading. Genetic modification has been practiced routinely for decades. SynBio is a new approach with a distinctly different approach and scope. This statement implies that all existing and historical GM research fits within the scope of SynBio.	Thank you for your comment. See our explanations added to section 3.3.3. Engineering was already part of GM; the term emerged in the late 1970 See our explanations added to section 3.3.3.

62	Nevoigt Elke, Jacobs University Bremen, e.nevoigt@jacobs-university.de, Germany	ABSTRACT	Recently, I already commented on the overlapping definitions of Biotechnology and SynBio. Here is a suggestion for a definition of SynBio (partially taken from existing definitions): SynBio is a sub-discipline of biotechnology which aims at the design, manufacture and/or modification of genetic materials in living organisms to alter living or non-living materials. The concept of SynBio goes beyond classical genetic engineering approaches with regard to its hallmark characteristics: predictable, off-the-shelf parts and devices with standard connections, robust biological chassis (such as yeast and E. coli) that readily accept those parts and devices, standards for assembling components into increasingly sophisticated and functional systems and open-source availability and development of parts, devices, and chassis. For me, it is most important that the definition clarifies that SynBio belongs to Biotechnology PLUS clarifies the unique features of SynBio (in contrast to traditional genetic engineering). The unique features might be better characterized by experts in the field of synthetic biology. My main concern is how the concept can be embedded into the existing definitions of biosciences, particularly (modern) biotechnology.	Thank you for your comment. SCs argue that the definition proposed is just shifting the problem: if we follow this advice we need to define the difference between classical GE and SynBio. The suggested hallmarks are very narrow and applicable only to a few prominent activities within SynBio; this approach would require an impractical *ad hoc* collection of hallmarks for every subfield within SynBio and would introduce a considerable bias towards currently widely publicized aspects, while risking to miss important minority developments.

63	Moll Nathalie, EuropaBio, n.moll@europabio.org, Belgium	ABSTRACT	Given the present public attention on synthetic biology, EuropaBio, the European association for BioIndustries, acknowledges the relevance for the European Commission to issue an opinion on this complex topic. EuropaBio members, involved in research, development, testing, manufacturing and commercialisation of biotechnology products and processes have been using recombinant DNA techniques for decades. Such activities are well and extensively regulated in many countries, including in particular in the European Union. Synthetic biology is a relatively new field, bringing together and building on a range of existing and new biotechnological tools. Currently, no common understanding exists on what synthetic biology is and therefore no legal definition has been agreed upon. In our opinion, the definition of synthetic biology proposed in the document (p. 27, lines 26-28: "SynBio is the application of science, technology and engineering to facilitate and accelerate the design, manufacture and/or modification of genetic materials in living organisms to alter living or non-living materials.") is not operational since it lacks discrete scientific criteria that would qualify a given research activity as synthetic biology. Indeed, according to such a definition, many techniques that have been in use over the past several decades in the EU could be wrongly construed as synthetic biology. Moreover, the proposed definition is incorrect given that it is based on the techniques used to develop synthetic biology products and not on the resulting products themselves. To accurately and appropriately address the next two mandated Opinions (risk assessment methodology, safety aspects and research priorities), the analysis must be based on the characteristics of the product which determine its safety, not	Thank you for your comment. See our explanations added to section 3.3.3. SCs argue that both the techniques and the resulting products are addressed in the definition. For example, an engineered SynBio cyanobacteria produces a product, it is bacteria and product that are products of SynBio. Therefore, it is important to address the techniques and the products, regardless of where and how it is deployed.

			the techniques which led to the product and which in themselves do not pose a specific safety hazard. In conclusion, EuropaBio would like to suggest that the European Commission consider making the definition of synthetic biology more specific and usable. An approach in line with the Minority Opinion (p. 30) regarding the definition of synthetic biology would provide a more practical, scientific and meaningful starting point for defining scientific biology. We recommend further dialogue with practitioners from industry, academia and society to assist in the development of a clearer definition.	

Contributions received through email

Comment 64	Scientific Committees Response
Sent: Tuesday, June 17, 2014 1:42 PM Subject: SynBio consultation Following your call forwarded to me, I would like to inform you that one of the National Academy of Technologies of France Fellows, Dr François Kepes, has already contributed the following comments related to the SynBio survey: *Dear Committee,* *I fully agree on the view of SynBio as a collection of conceptual and technological advances (Abstract). This statement should be made more central to the operational definition of SynBio as it justifies why SynBio has consequences that spread to all application fields of biotechnology.* *However, in my view the highlighted and repeated definition of SynBio in the Opinion is rather poor. "SynBio is the application of science, technology and engineering". For which purpose? "to facilitate and accelerate the design, manufacture and/or modification of genetic materials in living organisms". For which purpose? "to alter living or non-living materials." For which purpose? No answer, end of definition.* *I do not wish to add my own definition, just to point out that this one is little-informative and frustrating. Another aspect is that it fails to convey the essential information that SynBio is by necessity a cross-disciplinary domain. In this Opinion SynBio is presented as extreme genetic engineering. How about the computer scientists who present it as extreme computer science? Or, much more equilibrated and truthful, how about presenting it as a new domain at the crossroads of biology and mathematics/computer science?* *This Opinion also suffers from self-contradiction on the important issue of SynBio's concrete outputs. They are twofold, in vivo SynBio: GMOs (well discussed); and in vitro SynBio: protocells/nanoparticles/etc. Protocells (but no other in vitro SynBio expression such as e.g. nucleic acid-based boxes with conditional lids for drug*	Thank you for your comment. See answers to comment 9

delivery/galenics) are discussed on page 15. Good but insufficient. *Yet on page 27 it is stated that "SynBio as defined here excludes work on biological entities that are not capable of replication or of transferring genetic material". Well, a lot of the protocell work, in particular the applied one (galenics) and of the remainder of the in vitro SynBio is excluded by this statement. Thus, this exclusion statement on page 27 is at odds with the community understanding of SynBio and with the description on page 15 of protocells.* *Hope this is useful. Thank you for your attention,* *François KEPES* *http://www.issb.genopole.fr/~kepes/CVsynthbio.html* *http://www.biologie-de-synthese.fr/us-index.html* www.euro-case.org www.academie-technologies.fr "This e-mail is confidential and may contain legally privileged information. If you are not the intended recipient, you should not copy, distribute, disclose or use the information it contains. Please e-mail the sender immediately and delete this message from your system. E-mails are susceptible to corruption, interception and unauthorised amendment; we do not accept liability for any such changes, or for their consequences. You should be aware, that the company may monitor your emails and their content."	