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Update from EFSA's Synthetic Biology WG

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Trusted science for safe food

In 2012 EC commissioned 3 Scientific committees to deliver 3 opinions on Synthetic Biology:

- Scientific committee on Emerging and Newly identified Health Risks (SCENIHR)
- Scientific committee on Health and Environmental Risks (SCHER)
- Scientific committee on Consumer Safety (SCCS)

These opinions addressed:

- Definition of Synthetic biology
- Risk assessment methodologies and safety aspects
- Risks to the environment and biodiversity
- Research priorities in the field of SynBio

- The Scientific Committees (SCs) defined synthetic biology as “the application of science, technology and engineering to facilitate and accelerate the design, manufacture and/or modification of genetic materials in living organisms”.

- Scientific committees concluded that new SynBio developments may be assessed using current GMO RA methodologies. However, rapidly evolving technologies may require existing methodologies to be revisited at regular intervals and improved when necessary.
- In 2017 the Scientific Advice Mechanism (SAM) published an explanatory note which included an outline of possible agricultural applications of new techniques in the fields of Synbio

6 SynBio developments were assessed:

- Genetic part libraries and methods
- Minimal cells and designer chassis
- Protocells and artificial cells
- Xenobiology
- DNA synthesis and genome editing
- Citizen science (Do-it-yourself biology)

These technologies, methods and principles enable for faster and easier design and manufacturing of GMOs

EC asked EFSA for an opinion on GMOs developed through synthetic biology and their implications for risk assessment methodologies. The scope is limited to agri-food uses and requests EFSA:

- To reflect whether and which newer sectors/advances should be considered among **SynBio developments**, in addition to the 6 **identified**;
- To identify, where possible, potential risks in terms of impact on humans, animals and the environment for **current or near future** SynBio developments. Identify novel hazards as compared to established GMO techniques;
- To determine whether the **existing guidelines for risk assessment are **adequate and sufficient**** for current and near future SynBio developments or whether there is a need for updated guidance;
- In case guidances need to be updated, to identify the specific areas where such updated is needed.

- ToR Interpretations for the development of this opinion:
 - deliberate release into the environment
 - reaching the market in the next decade
 - exclusion of bioremediation applications (also de-extinction, bioweapons/biopreparedness, medical use , biofuels)
- Overarching mandate, encompasses different EFSA units (Agri/food uses);
- All relevant EFSA guidance documents for at least 6 SynBio developments for three organism groups (plants, animals, micro-organisms) will be considered;
- It was agreed with the EC to split up the mandate in different work packages.

Regulation

- Directive 2001/18/EC
- Implementing Regulation (EU) 503/2013
- Directive (EU) 2018/350

Guidance

- 2010 EFSA GMO Panel GD for ERA of GMPs
- 2011 EFSA GMO Panel GD for ERA of GMMs
- 2011 EFSA GMO Panel GD for RA of FF from GMPs
- 2018 EFSA FEEDAP Panel GD for the characterisation of microorganisms used as feed additives or as production organisms

- Two focused multidisciplinary **EFSA working groups** were established:
 - **Plant SynBio ERA**, chaired by Ewen Mullins
 - **GMM SynBio ERA**, chaired by Pier Sandro Cocconcelli
- Two **EFSA procurement contracts** reporting the results of literature searches for SynBio developments:
 - GMM:RIVM (NL), cecile.van.der.vlugt@rivm.nl
 - Plant SynBio ERA: JKI (DE), ralf.wilhelm@julius-kuehn.de
- **Assessment of GD based on SynBio case studies**, for applications likely to reach the market in 10 yrs; different complexity levels

- Products consisting or containing **viable genetically modified organisms**, as defined in Directive 2001/18 therefore able to replicate or transfer genetic material;
- GMMs covered include Archaea, bacteria, Eukarya;
- Products related to *“agri-food uses meaning agri/food/feed products falling within the remit of EFSA”*;
- Products **deliberately released into the environment** for experimental, scaling up or commercial reasons
- Product possibly **reaching the EU market during the next decade.**

- EFSA procurement contract NP/EFSA/SCER/2018/03 to Institute for Biosafety in Plant Biotechnology (SB), **Julius Kühn-Institut - Federal Research Centre for Cultivated Plants, Germany;**
- Literature search for plant SynBio developments in the agri-food sector;
- Final report delivered 30 April 2019 authored by: Katharina Unkel, Doerthe Krause, Thorben Sprink, Frank Hartung, Ralf Wilhelm;
- SynBio in plants is currently less advanced than in microorganisms

- Metabolic engineered plants will enter into market in the next 10 years (import to EU)



Continuous process of improving (stepwise) mainly less complex modifications (e.g. fatty acid composition) in already existing crops, to complex modifications incl. gene regulation using classical transgenesis and/or Genome Editing

many scientists would not consider this kind of work as being synthetic biology

- Only a few products (e.g. Flax for medical fiber) have been tested in Europe
- Changes in a plant`s fitness by altering transcription factors require intensive exploration before any market relevance can be considered
- Introducing improved carbon fixation systems (photosynthesis) in higher plants are currently basic research level.



SynBio in plants is still rare, therefore commercialization (time and products) is difficult to predict

Plant Expert's Mapping of plant SynBio developments

	Technology(s)	Description of the new trait (phenotype characteristics)	Plant Species Name/Crop	Level of complexity of the SynBio development (low, medium, high)	Level of complexity of the SynBio product (low, medium, high)	Degree of molecular modification (number of genes introduced)	Degree of molecular modification: number of endogenous genes modified: deletions, insertions, mutations (bp)	Final product	If relevant, comment on the comparator (currently used in conventional GMs).	Information on field trials, if relevant (small-scale/single year vs. large-scale/multiple years).	Geographic region (i.e. US, Canada, Australia, China, Japan)
1	Transgenes. (in future iterations the plant chassis may also be edited e.g. to increase yield)	Plants/plant cell cultures producing food additives - e.g. colour.	any plant	medium	low. Downstream processing needed	1-5	n/a (in future iterations the plant chassis may also be edited e.g. to increase product yield)	Purified or semi-purified extract. There will be no transgenic plant released.	wild-type cell cultures, plants	NO FIELD RELEASE - Cell culture, greenhouse	EU
2	transgenes	Plant food feedstocks engineered for increased nutrition - carotenoids e.g. astaxanthin	any crop	medium	low	1-10	n/a (in future iterations the plant chassis may also be edited e.g. to increase product yield)	Plant material/grains/seeds	wild-type plants	not yet (as far as we know)	EU
2	transgenes	Plant food or feedstocks engineered for increased nutrition - PUFAs (polyunsaturated fatty acids)	oil seed	medium	low	5-10	n/a (in future iterations the plant chassis may also be edited e.g. to increase product yield)	Plant material/grains/seeds	wild-type plants	https://www.ncbi.nlm.nih.gov/pubmed/27520497	EU
2	transgenes	Plant food or feedstocks engineered for increased nutrition - Amino acids, vitamin, proteins	any crop	medium	low	1-5	n/a (in future iterations the plant chassis may also be edited e.g. to increase product yield)	Plant material/grains/seeds	wild-type plants		WW
3	genome editing	Deletion of undesirable genes/produces, allergens - e.g. gluten	cereal	med	low		35-45 genes with point mutation in each (obtained with a single editing event)	Plant material/grains/seeds	in this example, CRISPR genes (Cas9 +sgRNAs introduced, iterations the plant chassis may also be edited e.g. to increase product yield)	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5867031/	USA & EU
									wild-type - however		

- Technology:
 - Transgenes
 - Genome editing
- New trait:
 - Plant food feedstocks for increased nutrition
 - Carotenoids, PUFAs, low gluten
 - Plants with engineered complex traits
 - Yield, tolerance to biotic and abiotic stress
- Number of genes introduced:
 - 1-10, 5-10, Cas9 +sgRNAs introduced (not present in final product), 1-20

1. Plant food/feedstock for Increased nutrition; introducing Vitamin B12 pathway in plants (>15 genes)

<https://doi.org/10.1038/nchembio.1086>

2. Deletion of undesirable gene product e.g. Allergenicity – low gluten by CRISPR mutagenesis

[Plant Biotechnol J. 2018 Apr; 16\(4\): 902–910.](#)

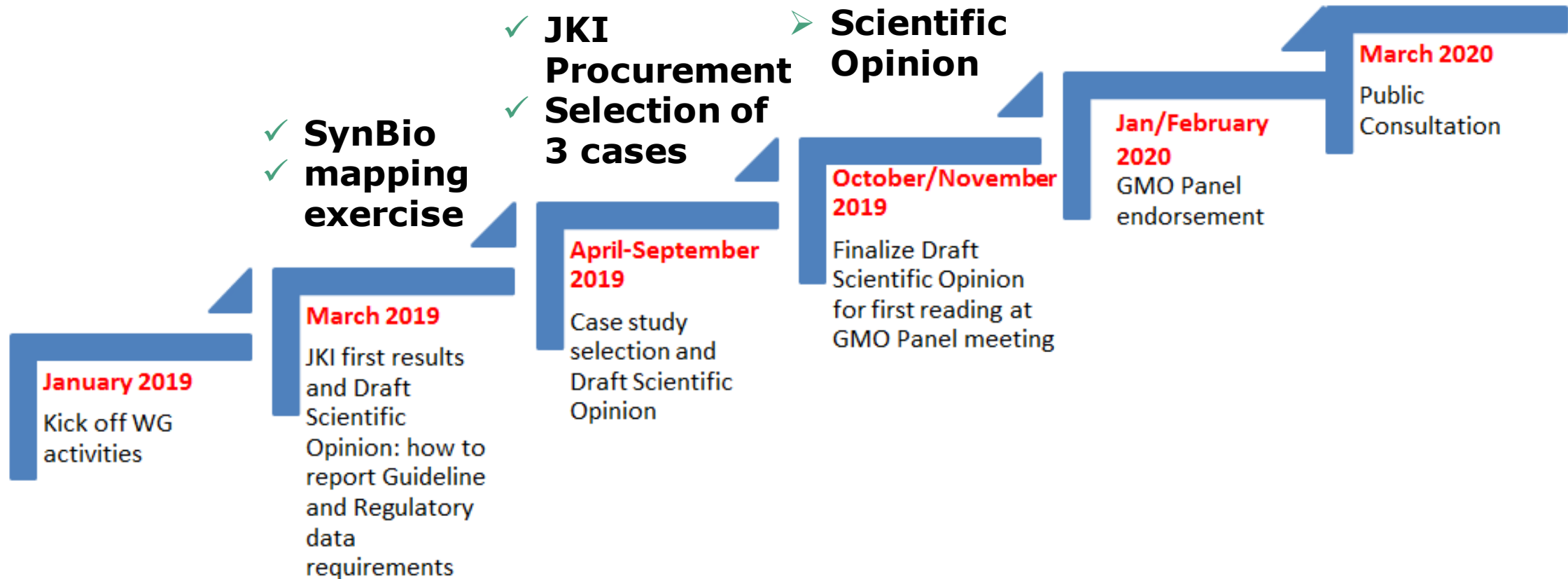
3. Plants with engineered complex traits – immunity. Addition of synthetic resistance genes (endogenous resistance proteins engineered to respond to an expanded range of pathogen proteins AND CRISPR mutations of endogenous susceptibility genes)

<https://www.biorxiv.org/content/10.1101/611152v1>

- Scientific opinion on the adequacy of the guidance for ERA of GM plants, including MC;
- Scientific opinion on the adequacy of the guidance for category 4 GMMs for MC and ERA;
- By end of 2020, publication of final opinion after public consultation

In a later phase of this mandate other guidances will be assessed for their applicability for SynBio applications

Progress of SynBio Plant ERA WG








Next core meetings:

- June 20
- October 25







- **EFSA's SC and SCER Unit: project coordination**
 - Caterina Barasso (GMM WG Contact point)
 - Reinhilde Schoonjans
- **EFSA staff: project contribution**
 - Jamie Aguilera (ERA, GMM)
 - Support Units: ALPHA, PPR, NUTRI, FEED, FIP and GMO
- **GMO Unit: Plant SynBio ERA coordination:**
 - Yann Devos (ERA)
 - Nikoletta Papadopoulou (MC, Plant ERA Contact point)
 - Tommaso Raffaello (MC, GMM)
- **GMO experts:** Ewen Mullins (chair), Josep Casacuberta, Tamas Dalmay, Antoine Messean, Adinda De Schrijver
- **Plant SynBio ERA WG Experts:** Nicola Patron, Matias Zurbriggen

■ GMM WG

Experts		
Name	Role	Declaration of Interest
COCCONCELLI Pier Sandro	Chair	DoI 
GLANDORF Boet	Member	DoI 
HERMAN Lieve	Member	DoI 
TEBBE Christoph	Member	DoI 

Other invitees		
Name	Role	Declaration of Interest
DE LORENZO Victor	Hearing Expert	DoI 

■ Plant SynBio ERA WG

Experts		
Name	Role	Declaration of Interest
CASACUBERTA Josep	Member	DoI 
DALMAY Tamas	Member	DoI 
DE SCHRIJVER Adinda	Member	DoI 
MESSEAN Antoine	Member	DoI 
MULLINS Ewen	Chair	DoI 
PATRON Nicola	Member	DoI 
ZURBRIGGEN Matias	Member	DoI 