The Regulation of Synthetic Biology by EU Law: Current State and Prospects

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Abstract Assuming that synthetic biology (SynBio) will generate not only new benefits but also new risks to human health and the environment this article explores to what extent SynBio is already adequately supervised by the existing EU regulation of genetically modified organisms (GMOs). While the GMO regime is applicable to many kinds of SynBio activities, others are not covered, such as the complete replacement of the genetic material of a cell, the insertion of transgenes into an organism by other methods than those listed as qualifying as genetic engineering—or not—the construction of a protocell and minimal cell, the placing on the market of bioparts, and xenobiochemistry. The article then asks if the risk assessment methodology applicable to GMOs is suited for products from SynBio. This question is denied insofar as the familiarity principle which governs traditional GMO risk assessment is concerned. New and genuine methodology must be developed to identify hazards and evaluate risks. While the thrust of the article is on ex ante regulation, or administrative oversight, it also discusses ex post regulation, or civil liability for damage, concluding that liability schemes must also be adapted to the new characteristics of SynBio. In sum, it is time for regulators to take a closer look at SynBio.

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1 Introduction

Synthetic Biology (SynBio) is being heralded for generating new benefits for society. These include such diverse areas as medicine, energy, fine chemicals, food, materials, environmental engineering, agriculture and even computer technology (Baldwin et al. 2012, Chap. 7; Church and Regis 2012). But it is also likely to cause drawbacks. Artificially designed and synthetically compiled organisms or genetic parts of them may escape containment, or may deliberately be released, and cause adverse effects to human health or the environment. Regulation is the major means of preventing this.

The prevention by regulation of such risks means that actors in research, development, production, trade and use of SynBio are subjected to a set of duties of caution concerning the effects on third parties or public goods. The fulfilment of theses duties is supervised by administrative bodies and liability for damages. Third parties may be given rights to claim protection against risks or compensation for damage.

The regulation can be ex ante or ex post, ex ante meaning that administrative oversight is involved before an activity may be undertaken, and ex post that the party is liable for any damage caused by his/her activities.

2 Regulation Ex Ante

Most closely related to SynBio is the legal regime on genetically modified organisms (GMOs). Other regimes (which are not considered here) are the regulation of chemicals and that of pathogens. The GMO regime consists of both EU and MS legislation. It is basically structured according to whether GMOs are handled in containment, or intentionally introduced into the environment, be it through release at a predetermined site or, after they have been placed on the market, through introduction anywhere.

In the EU any works or products based on genetic modification are subjected to a special legal regime for GMOs. In contrast, in the US processes and products are checked as part of the control regime for non-modifying processes and non-modified products. For instance, a genetically modified pesticide would in the EU need two market placement authorizations, one under the GMO and the other under the pesticides legislation, and in the US just one under the pesticides legislation (Lynch and Vogel 2001).

Before considering whether the EU's GMO regime is an appropriate regulatory tool for SynBio we need to examine if, and to what extent, the existing EU GMO regulatory regime is applicable to SynBio at all.

2.1 Applicability to SynBio of the GMO Regime

The GMO regime is, as already mentioned, applicable to the "contained use," the individual "release" and the wider "placing on the market" of "GMOs." The regulation of contained use is harmonized EU wide only in relation to genetically

modified microorganisms (GMMs).[1] Contained use of other GMOs is thus left to the regulatory competence of the Member States (MS).[2] In contrast, the regulation of the release and placing on the market of GMOs is standardized by EU legislation concerning all kinds of GMOs.[3] In any case, the core notion triggering the regulatory regime is a GMO. Its legal definition must therefore be explained and applied to SynBio techniques. The legal definition varies to some degree in relation to GMOs in general and GMMs, but the differences are not important in the present context.

An "organism" is legally defined as

> any biological entity capable of replication or of transferring genetic material.[4]

This already excludes any modified or artificial subcellular bioparts that are not capable of replication from the application of the GMO regime.

Further, a genetically modified organism is defined as

> ...an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.[5]

Thus, for a GMO an organism must exist that is modified in certain artificial ways. For SynBio, this means that the GMO-regime only deals with activities which start with a real organism and modify it in specified ways. This excludes from the regime the complete synthesis of a known organism as well as the completely new design and synthesis of a new organism. In particular, bottom-up constructed protocells are not covered by the GMO regime.

The third element of the definition of a GMO is that the "genetic material" of the organism has been altered. The term "genetic material" undoubtedly includes the DNA and arguably also the RNA, considering the fact that the mRNA and tRNA, switched on by a gene, are part of the information process initiating the production of amino acids and through them of proteins. However, if by methods of the so-called xenobiochemistry (Budisa 2012) the amino acids are replaced by non-natural ones, and thus, new proteins emerge creating hitherto unknown properties of the organism, the operation is not one altering the "genetic material."

The fourth element is that the genetic material contained in the organism was "altered". This poses the question if "alteration" also includes the complete

[1] Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms (Recast), OJ L 125, 21.5.2009, p. 75, Art. 1.

[2] The German Act on Gene Technology (Gentechnikgesetz—GenTG), for instance, extends its provisions on contained use to all GMOs. It however empowers the government to exempt those GMOs which are considered to be safe (Sect. 2a GentG).

[3] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC, OJ L 106, 17.4.2001, p. 1, Art. 2 (1).

[4] Art. 2 (1) Directive 2001/18/EC.

[5] Art.2 (2) Directive 2001/18/EC.

replacement of the genome of a cell, such as in the experiment with mycoplasma bacteria of the Craig Venter Institute (Gibson et al. 2010). Based on a teleological reading this would, because of the unknown risks, need to be controlled even more than the mere modification. However, in a literal interpretation the full replacement is different from a mere alteration. Man may ask if this should be different in the case in which the inserted material consists of newly synthesized conventional components. But in this case the organism is not altered but remains the same both chemically and functionally.

The fifth element is that the nucleic acid molecules inserted into a host organism may have been "produced by whatever means outside an organism."[6] Thus, not only traits from existing organisms or a synthesized copy of them are covered, but also synthesized traits having a new design, such as those generated by the so-called xenobiology (Schmidt 2010; Budisa 2012).[7] This means that xenobiology insofar it induces artificial DNA or RNA is included in the GMO regime.

The sixth element is that that nucleic acid molecules must be *inserted* into a host organism. This excludes from the GMO-regime methods of reducing organisms to minimal cells because in this case genetic material is removed from, rather than added to, the organism.[8]

The seventh element, as mentioned, is that the alteration of the genetic material is done "in a way that does not occur naturally by mating and/or natural recombination".[9] The core techniques qualifying as not natural are listed in Annexes to the relevant directives. They include, inter alia, the insertion of nucleic acid molecules by means of a vector system into a host organism in which they do not naturally occur, or by direct introduction such as micro-injection, or by not naturally occurring cell fusion or hybridisation.[10] This implies, for instance, that the gene gun method used in the do-it-yourself networks (DIY-Bio) is un-supervised.[11]

In contrast to the positive list of techniques qualifying as genetic engineering, certain techniques are excluded from the GMO regime because although being more or less artificial they can (at least theoretically) also occur under natural conditions. These techniques are mutagenesis and certain kinds of cell fusion.[12] However, a whole bunch of "New Plant Breeding Techniques (NPBTs)"—arguably included in a broad understanding of SynBio—have been developed that although in

[6] Directive 2001/18/EC Art. 2 (2) together with Annex I A Part I (1).

[7] This technique was however, not unknown to earlier genetic engineering. For instance, the gene which encodes the PAT-protein and conveys tolerance of the herbicide glyphosinate was redesigned and thus differs from the natural PAT-gene. Example taken from (Bundestag 2011). The radical version would be the above cited mycoplasma experiment.

[8] For a description of this technique see (Budisa 2012, pp. 103–108).

[9] Art.2 (2) Directive 2001/18/EC.

[10] Directive 2001/18/EC Art. 2 (2) together with Annex I A Part I (1)–(3).

[11] How naïvely the networks operate can be studied from the video displayed at http://www.sueddeutsche.de/wissen/biohacking-bewegung-leuchtende-pflanzen-zum-selberbasteln-1.1875586-2 (visited 14.02.2014).

[12] Directive 2001/18/EC Annex I B.

Table 1 Defining GMOs in application to SynBio

Elements of definition	Elements not covered
The GMO must be an organism	Bioparts
The GMO must derive from an organism	Complete synthesis of an organism; bottom-up construction of a protocell
The genetic material must be altered	Complete replacement of the cell content, be it with conventional or new design
The inserted transgenes can be of any design and construction method	
Transgenes must be "inserted"	A minimal cell
Positive and negative lists of techniques of insertion	Not listed techniques (e.g. gene gun), new breeding techniques

principle "natural" are so deeply interfering that they can be as hazardous as GMOs in the legal sense. Such techniques include targeted site-specific mutagenesis, transgenesis as an intermediate step of breeding processes where the transgene is subsequently removed, or "cisgenesis" where genes from the same species or family are transferred (Parisi 2012; Raaijmakers 2009). Thus, a substantial part of new breeding techniques appear not to be captured by the EU GMO regime (Table 1).

In conclusion, SynBio, insofar as it works on existing living cells and alters their genetic material in a way that does not occur naturally, must be counted as a technique resulting in genetic modification and thus as subjected to the existing EU GMO regime. In particular, organisms in which the genetic content was modified by synthesized material of natural or artificial design are covered, even insofar as new genetic xeno-material is introduced. By contrast, the following SynBio products are not captured by the GMO regime:

- an organism which was synthesized, be it of natural or artificial design
- an organism in which the genetic material was completely replaced by known or artificial genetic material
- an organism into which genetic material was inserted by other techniques than vector systems, micro-injection, non-natural cell-fusion or hybridization
- an organism whose chemical derivatives (amino acids, proteins) were modified
- a protocell
- a minimal cell
- synthesized or extracted bioparts
- an organism whose chemical derivatives (amino acids, proteins) were modified by xenobiochemistry
- an organism resulting from new breeding techniques which although in principle naturally occurring are deeply interfering.

It appears that this result—important SynBio techniques not being covered by the GMO regime—is not adequately discerned by research institutions and governments.[13]

[13] See for Germany (Acatech et al. 2009, p. 34); (Bundestag 2011).

There are two ways of reacting to the fact that parts of SynBio escape the scope of the existing GMO regime: One is to widen the scope so that more areas of SynBio are covered, and the second is to introduce a new law. The first option is certainly easier to reach politically, but the second would be more appropriate because it could be based on a new approach which better matches instruments of administrative oversight with different categories of risk. This approach could even reflect the fact that some kinds of genetic modification qualify to be released from any prior regulation while others which are presently need to be subjected to it.

2.2 Adequacy of the GMO Regime

We now proceed to consider what principles of risk assessment are appropriate for SynBio. This shall be done by critically reviewing the risk assessment methodology that is presently applicable to GMOs. If they are found to be inappropriate, better methodologies for SynBio must be introduced either by the existing legal regime as enlarged in scope, or the new regime if that is established.

Products from synthetic biology, or SynBio products (SBPs)[14] will probably be fabricated and used in contained systems for a long time to come. Therefore, the relevant EU legal acts on contained genetic engineering operations must be consulted for their adequacy for SBPs. However, it is also possible that SBPs will be developed that shall intentionally be introduced into the environment, such as microorganisms for the treatment of contaminated water or soil; or for the production of energy from biomass (French 2014). It is less probable that SBPs will be placed on the market for random release, in the near future. But the possibility exists, for instance for microorganisms constructed for environmental management or energy fabrication. It must also be considered that a vibrant market has emerged for bioparts which provides services for contained R&D in SynBio. We will therefore first explore the regime for contained operations, and then the deliberate release of SBPs at certain locations as well as their market placement.

2.2.1 Contained Use

As already indicated, EU law on contained use of GMIOs only refers to genetically modified microorganisms (GMMs) leaving other GMOs to the legislative competence of the member states.

[14] I suggest the introduction of this term into the emerging debate on a regulatory scheme for SynBio. Alternatively one could consider "SynBio organism" (SO) as the core·term, but this would not cover bioparts.

Risk Paths

Even if kept in containment, GMMs may cause risks for the researchers and workers. Moreover, they may unintentionally leak into the environment through persons carrying them out of the lab, or through solid waste, sewage or exhaust disposed from the lab. The same paths must be considered for SBPs.

Protected Goods

According to Art. 4 Directive 2009/41/EC Member States

> ...shall ensure that all appropriate measures are taken to avoid adverse effects on human health and the environment which might arise from the contained use of GMMs.

The goods protected by the GMM regime are thus human health and the environment. Any "adverse effect" to them must be avoided.

Although this is not explicitely mentioned in the directive it has been discussed whether besides preventing risks GMMs must also provide a socio-economic benefit. When in the late eighties and early nineties the first facilities with contained systems were built for research on dangerous microorganisms, concerns were raised if the containment would be perfect enough to hinder any escape of GMMs. Considering that a residual risk of leakage cannot be avoided, it was debated if the unavoidable remaining risk should not be weighed against the benefits generated by the GMM. For instance, in a hearing on the construction of a BASF facility for the production of the pharmaprotein Tumor Necrosis Factor (TNF) a concerned citizen argued that TNF was ineffective if not detrimental as a medicinal drug so that the construction of a production unit for TNF constituted, as she called it, a senseless risk (cf. Winter et al. 1993, p. 34). Since then, the discussion about weighing risks against social benefits (or their absence) has faded away in relation to contained systems. It has however continued in relation to the deliberate release and market distribution of GMOs.[15]

Concerning highly problematic kinds of SBPs the same discussion may be reopened even in relation to contained systems.

Burden of Submission of Risk Related Data

Risk assessment is only possible if appropriate data are available. Generally, in administrative proceedings the authorities are responsible for collecting the relevant data (investigation principle).[16] Ultimately, this rule rests on the fundamental right to individual freedom, which implies that if a law imposes restrictions based on certain factual circumstances these facts must be identified and proven by the competent authority.

[15] See further below.

[16] See Art. 337 TFEU and (v. Danwitz 2008, pp. 417–421).For Germany see Sect. 24 Administrative Procedure Act (Verwaltungsverfahrensgesetz—VerwVfG).

The burden of producing evidence can however be imposed on the individual by special legislation. This normally occurs, if an activity requires prior authorization or notification, because it is assumed that the activity is suspected to pose a risk and shall therefore only be allowed after detailed examination. The EU GMM regime is based on this assumption and therefore shifts the burden of data provision to the applicant.[17] It specifies which data have to be presented, limiting the scope to those data which are needed to assess whether the substantive protective standard (the protection of human health and the environment) is met.[18]

If the presented data are not sufficient to allow a prognostic assessment, the competent authority can request the submission of additional data.[19] If the available knowledge is not sufficient for this purpose, the applicant bears the burden of generating it, provided there are indications of risk.[20]

Knowledge relevant to an authorisation or notification proceeding may already be held by the administrative authority. If that is the case, the authority must make use of it in the authorisation procedure and cannot ask the applicant to reproduce it anew.[21]

It appears that these principles of data submission would also fit if an authorisation regime for using SBPs in contained systems was introduced.

List of Data to Be Submitted

In the case of contained use of highly hazardous GMMs the data to be submitted by the applicant comprise the following[22]:

(a) [...]

(b)

- the recipient or parental micro-organism(s) to be used,
- the host-vector system(s) to be used (where applicable),
- the source(s) and intended function(s) of the genetic material(s) involved in the modification(s),
- the identity and characteristics of the GMM,
- the culture volumes to be used;

[17] It is true, however, that Directive 2009/41/EC allows for exempting from its scope those GMMs which are considered to be safe (Art. 3 (1) (b) together with Annex II Part C of the same directive).

[18] Arts. 6–9 Directive 2009/41/EC.

[19] Art. 10 (3) (a) Directive 2009/41/EC.

[20] This requirement can be based on Art. 4 Directive 2009/41/EC as interpreted in view of the precautionary principle according to Art. 191 (2) (2) Treaty on the Functioning of the European Union (TFEU). On the necessity of indications and thus the exclusion of a zero risk approach see European Court, Case T-13/99, judgment of 11 September 2002 (Pfizer), paragraphs 144–148.

[21] See the clause "if necessary" in Art. 10 (3) Directive 2009/41/EC.

[22] Directive 2009/41/EC, Annex V Part C.

(c)

- a description of the containment and other protective measures to be applied, including information about waste management, including the type and form of wastes to be generated, their treatment, final form and destination,
- the purpose of the contained use, including the expected results,
- a description of the parts of the installation;

(d)

- information about accident prevention and emergency response plans, if any,
- any specific hazards arising from the location of the installation,
- the preventive measures applied, such as safety equipment, alarm systems and containment methods,
- the procedures and plans for verifying the continuing effectiveness of the containment measures,
- a description of information provided to workers,
- the information necessary for the competent authority to evaluate any emergency response plans, if required under Article 13(1);

While the data listed sub (c) and (d) might be transferable to the situation of hazardous SBPs those sub (b) reflect the fact that the object of assessment is genetic modification of existing organisms. This may be appropriate for SBPs that are based on existing organisms. However, for new SBPs lists of required data must be developed that are better targeted to the specific risks of such SBPs. Where interpolations from donor, vector and recipient organisms are not possible specific tests concerning the resulting organism must be required. Moreover, as the GMO regime only covers living organisms, risks from bioparts, individually and in combinations, are not addressed by the data list.

Assessing and Categorising Risk and Containment

Risk prevention measures should differ depending on the severity of the risks caused. The more hazardous the use of an organism is the tighter the containment must be. This is also the logic applied in the EU GMM regime. Four risk categories are distinguished corresponding to an increasing intensity of containment measures. These categories are described as Class 1: no or negligible risk, Class 2: low risk; Class 3: moderate risk; and Class 4: high risk. The four risk classes are correlated with four containment classes. These consist in clusters of measures concerning the construction of the lab (e.g. isolation), the equipment (e.g. negative pressure), the system of work (e.g. restricted access, clothing), and the treatment of waste (e.g. inactivation of GMMs). [23]

[23] Art. 4 (3) and Annex IV of Directive 2009/41/EC.

The risk assessment serves to classify any use of GMMs into one of the four risk and containment classes. A two-step procedure is recommended for this exercise[24]:

- Procedure 1
  Identify potentially harmful properties (hazard) of the GMM and allocate the GMM to an initial class (class 1 to class 4), taking into account the severity of the potentially harmful effects.
  and
  Assessment of possibility of harmful effects occurring by consideration of exposure (both human and environmental), taking into account the nature and scale of the work, with containment measures appropriate to the initial class allocated.
- Procedure 2
  Determination of final classification and containment measures required for the activity. Confirm final classification and containment measures are adequate by revisiting Procedure 1.

When assessing the risk of the resulting GMO, the hazards of the donor as well as the resulting organism must be considered, i.e.[25]:

1. the recipient micro-organism;
2. the genetic material inserted (originating from the donor organism);
3. the vector;
4. the donor micro-organism (as long as the donor micro-organism is used during the operation);
5. the resulting GMM.

The following endpoints must be examined[26]:

Human health considerations:

- expected toxic or allergenic effects of the GMM and/or its metabolic products,
- comparison of the modified micro-organism to the recipient or (where appropriate) parental organism regarding pathogenicity,
- expected capacity for colonisation,
- if the micro-organism is pathogenic to humans who are immunocompetent,
- diseases caused and mechanism of transmission including invasiveness and virulence,
- infective dose,

[24] Commission Decision of 27 September 2000 concerning the guidance notes for risk assessment outlined in AnnexIII of Directive 90/219/EEC on the contained use of genetically modified micro-organisms, Annex Nr. 2.

[25] Annex III A (2) Directive 2009/41/EC.

[26] Commission Decision of 27 September 2000 concerning the guidance notes for risk assessment outlined in AnnexIII of Directive 90/219/EEC on the contained use of genetically modified micro-organisms, Annex Nr. 3.2.5.

- possible alteration of route of infection or tissue specificity,
- possibility of survival outside of human host,
- biological stability,
- antibiotic-resistance patterns,
- allergenicity,
- toxigenicity,
- availability of appropriate therapies and prophylactic measures.

Environmental considerations:

- ecosystems to which the micro-organism could be unintentionally released from the contained use,
- expected survivability, multiplication and extent of dissemination of the modified micro-organism in the identified ecosystems,
- anticipated result of interaction between the modified micro-organism and the organisms or micro-organisms which might be exposed in case of unintentional release into the environment,
- known or predicted effects on plants and animals such as pathogenicity, toxicity, allergenicity, vector for a pathogen, altered antibiotic-resistance patterns, altered tropism or host specificity, colonisation,
- known or predicted involvement in biogeochemical processes.

These parameters will have to be revisited in relation to SBPs. Based on accumulated experience, lists of typical organisms and treatments have been compiled for GMMs. However, concerning SBPs, it is questionable if the research activities can already be categorized in a like manner. They are still very diverse, and risk related knowledge is scarce. Moreover, the risk classes and containment measures mainly refer to the hazards of the donor and receiver organisms. It appears that for the more radical interventions of SynBio into the genome, genuine methods of assessment must be developed. This is all the more the case in relation to bioparts, protocells and minimal cells. Obviously, more discussion with scientists is needed in this regard.

2.2.2 Introducing SBPs into the Environment and Placing SBPs on the Market[27]

As already indicated, EU legislation, and in particular Directive 2001/18 categorises the introduction of GMOs into the environment as the deliberate release at a particular site and the introduction into the environment at any site after GMOs have been placed on the market. Both the release and the placing on the market must be authorised. [28] An authorisation of market placement of a GMO implies the subsequent introduction into the environment at any location, unless the allowable

[27] The following analysis is based on (von Kries and Winter 2012).

[28] Articles 5 and 6; 13–15 Directive 2001/18/EC which provide differentiated procedures of notification, risk assessment, commenting and final decision.

locations are restricted by conditions of the authorisation. [29] Concerning genetically modified food and feed, including seeds, a special regime has been established which takes precedence over the general regime which will however not be treated in this article because SynBio is still far from involving food and feed.[30]

We can treat the deliberate release and the market placement together because the risk prevention criteria and risk assessment methodologies are largely the same for both activities, with certain variations due to the larger geographical scope of introductions into the environment of GMOs which are authorised for market release.

Risk Paths

According to Art 4 (3) Directive 2001/18/EC Member States shall ensure that potential adverse effects on human health and the environment, which may occur directly or indirectly through gene transfer from GMOs to other organisms, are accurately assessed on a case-by-case basis.

Correspondingly, an environmental risk assessment (ERA) must evaluate risks

> whether direct or indirect, immediate or delayed, which the deliberate release or the placing on the market of GMOs may pose … [31]

The distinction between direct and indirect effects means that not only those adverse effects caused by GMOs in direct contact with endpoints (e.g., a human being, animal or plant absorbing a GMO) have to be prevented but also those which are mediated by intervening factors. Annex II of Directive 2001/18/EC defines indirect effects as follows:

> "indirect effects" refers to effects on human health or the environment occurring through a causal chain of events, through mechanisms such as interactions with other organisms, transfer of genetic material, or changes in use or management.

On this basis one could differentiate indirect effects further into natural causal chains (horizontal and vertical gene transfer, food chain, etc.) and chains mediated by human practices (such as agricultural change in pesticide use and crop rotation, etc.).

Concerning the distinction between immediate and delayed effects, the Commission Guidance on the environmental risk assessment gives examples for delayed effects such as the GMO developing invasive behavior, several generations following its release.[32]

[29] Parts B and C of Directive 2001/18/EC.

[30] Regulation (EC) No 1829/2003 of the European Parliament and of the Council of 22 September 2003 on genetically modified food and feed (Text with EEA relevance), OJ L 268, 18.10.2003, p. 1.

[31] Art 2 (No 8) Directive 2001/18/EC.

[32] Guidance Notes on the Objective, Elements, General Principles and Methodology of the Environmental Risk Assessment Referred to in Annex ii to DIRECTIVE 2001/18/EC, OJ L 18, 07.11.2003, p. 32.

In addition to alerting the risk assessment to direct/indirect and immediate/delayed effects the ERA must also consider different environments exposed to the GMO[33]:

> For each adverse effect identified, the consequences for other organisms, populations, species or ecosystems exposed to the GMO have to be evaluated.
>
> Moreover, there may be a broad range of environmental characteristics (site-specific or regional-specific) to be taken into account. To support a case-by-case assessment, it may be useful to classify regional data by habitat area, reflecting aspects of the receiving environment relevant to GMOs (for example, botanical data on the occurrence of wild relatives of GMO plants in different agricultural or natural habitats of Europe).

This rather ambitious programme, relating to genetically modified plants, was further elaborated by Guidance of 2010 of the European Food Safety Agency (EFSA).[34] It concentrates on interactions of the plant on the levels of organisms and ecosystems.[35]

While this analytical framework looks comprehensive, a note of caution is, however, appropriate: The fate of the GMO in the various environments may prove to be too complex to be examined. This is particularly true if the GMOs introduced into the environment are microorganisms. It is telling that in that regard the pertinent EFSA Guidance somewhat wearily states as follows:

> Predicting impacts of GMMs and derived food or feed on complex ecosystems can be difficult due to continuous flux and spatial heterogeneities in ecosystems creating a myriad of potential microbial habitats in which interactions between GMMs and their products with the indigenous organisms and/or abiotic components can take place. It is recognised that an ERA cannot provide data of a GMM or its products, which would cover all potential environmental habitats and conditions. Consideration of environmental impact (damage) should, therefore, focus on environments in which exposure is most likely or in which, when relevant, viable GMMs could potentially proliferate.

Protected Endpoints

Human health and the environment

EU law has established that, for the deliberate release of GMOs, as well as for contained use, the protected goods shall be human health and the environment. These shall be kept safe from 'adverse effects. 'All appropriate measures' must be taken to prevent these.[36]

[33] Annex II Directive 2001/18s. 4.2.2 and Commission Guidance Sect. 3 3rd hyphen.

[34] (EFSA 2010).

[35] See further on a multilevel approach of risk assessment of GMOs and SBPs (Breckling and Schmidt 2015, this volume).

[36] Art. 4 Directive 2001/18/EC.

What are adverse effects? Is the mere presence of a GMO outside the field of release, per se, to be considered as adverse effect? Prevailing court practice and doctrine negate this. They posit that the adverse effect must be a result of such presence, like the damaging of non-target species from an insecticide plant. The justification given is that the law only addresses the specific risks of genetic engineering, which shall be only health and environmental risks.[37]

Concerning SBPs this might be seen differently. It could be argued that given the early stage of R&D in this area and the radically artificial nature of SynBio, SBPs should not be allowed to spread at all. Any release would then have to be contained. Alternatively, if SBPs were constructed to only survive under artificial conditions, one could consider their safe release into the environment, because they would immediately die off there. However, this would not apply to organisms which are intended to survive and perform in the open environment.

Socio-economic benefits

GMO releases may create benefits for the producer and consumer. Is this to be weighed against the risks to human health and the environment? Such an analysis is envisaged in the genetic engineering legislation of some countries.[38] It is, however, only scarcely present in European GMO legislation.[39]

When pursuing this request two brands of risk-benefit-consideration should be distinguished: a risk-tolerating variant which would allow any risk that is outweighed by benefits, and a risk-averse variant according to which only residual risks can be outweighed by benefits. An example, for instance, of the second variant would, in relation to seeds, be the agricultural benefits of certain genetic modifications, such as the subsequent non-use of pesticides, the use of less water and reduction of chemical fertilizers. Thus, a residual risk to certain parts of the environment could become acceptable, if the overall eco-balance of agriculture were to be improved.

Concerning the release of SBPs into the environment, socio-economic benefits should also be introduced as an additional requirement; but only after its risks

[37] See for Germany Administrative Court (VG) Berlin, decision of 12.09.1995—14 A 255.95, in: Eberbach/Lange/Ronellenfitsch, Recht der Gentechnik und Biomedizin, Entscheidung Chap. 4 on § 16 GenTG; VG Braunschweig, judgment of 12. 9.1995—14 A 255.95, No. 27.

[38] For Germany see § 16 paras. 1 und 2 GentG, according to which "harmful effects on the protected goods listed in § 1 No. 1 must not be incurred if unacceptable in view of the objective of the release." Unacceptability in view of the release objective can be understood as a kind of weighing risk versus benefit. German scholars tend to reject such interpretation, arguing that this would be incompatible with the relevant EU law. See also Art. 10 of the Norwegian Gene Technology Act: "In deciding whether or not to grant an application, considerable weight shall also be given to whether the deliberate release will be of benefit to society and is likely to promote sustainable development." This provision has, however, rarely been applied in practice (Spök 2010).

[39] See the rather enigmatic opening clause ("... other legitimate factors") in Art. 7 and 19 of Regulation (EC) 1829/2003.

where assessed and found minimal, not as a vehicle to outweigh significant risks by higher valued benefits.

Cultural factors

The rejection of GMOs by the majority of the population in a number of countries can be explained by cultural factors. This skepticism is based on a conglomerate of concerns including extreme precaution, criticism against neglecting the evolutionary wisdom, doubts about whether the promised benefits are not already available from existing organisms, political will as well as ethical concerns and religious beliefs. The cultural factor is not well represented in national and international law as a legitimate justification for trade restriction. For instance, it was not even considered in the resolution of the WTO panel on EC restrictions concerning the marketing of biotech products.[40]

The ECJ has shown understanding for the cultural factor in *Commission versus Poland* but finally rejected it by splitting the issue into three parts: Insofar as extreme precaution was alleged, the Court said that this does not dispense from the normal standard applied in the EU; concerning the opponent political will it held that the MS must neglect it once an EU legal act has been adopted; and concerning ethical and religious beliefs it held that the strength and spread thereof was not sufficiently proven. [41]

It is submitted that the cultural factor should be given a more legitimate place in regulatory designs.[42]

Data to be submitted

A long list of data has been compiled that must be submitted for an application for release of GMOs. It comprises[43]:

- Information relating to the GMO
- Characteristics of (a) the donor, (b) the recipient, or (c) (where appropriate) parental organism(s)
- Characteristics of the vector
- Characteristics of the modified organism
- Information relating to the conditions of release and the receiving environment
- Information relating to the interactions between the GMOs and the environment
- Information on monitoring, control, waste treatment and emergency response plans

[40] WT/DS 291, 292/293/ R 29 Sept. 2006.

[41] ECJ Case 165/08, judgment of 16 July 2009 (Commission v Poland) paragraphs 54, 55, 58, 59.

[42] See further (Pardo Avellaneda 2014 forthcoming).

[43] Annex III of Directive 2001/18/EC.

This list would have to be thoroughly checked for its suitability for SBPs releases. Once again, it must be considered that more and more research is aiming at replacing traits from parental organisms by synthesis and, even more importantly, by artificial design.

The ERA, as outlined by Annex II Directive 2001/18/EC, focuses on those paths of risk with human health and the environment as endpoints. Other endpoints, like the coexistence with non-GM agriculture, the economic benefit and political as well as cultural values, are hardly considered (Dolezel et al. 2009, p. 27). However, should these aspects become a legally required part of the risk management, then information has to be provided and assessed which is methodologically clear and rich in substance.

The stepwise generation of knowledge

Towards the end of the nineteen-eighties, when the deliberate release of GMOs was approached, knowledge about the involved risks was still highly undeveloped. Even today, there remain gaps in our knowledge. Nonetheless, to enable the release of GMOs and acquire knowledge, the step-by-step principle was introduced: incremental generation of knowledge in parallel with decreasing containment of tests.[44]

The step-by-step principle is characterised by recitals (24) and (25) Directive 2001/18/EC as follows:

> The introduction of GMOs into the environment should be carried out according to the "step-by-step" principle. This means that the containment of GMOs is reduced and the scale of release increased gradually, step by step, but only if evaluation of the earlier steps in terms of protection of human health and the environment indicates that the next step can be taken.
>
> No GMOs, as or in products, intended for deliberate release are to be considered for placing on the market without first having been subjected to satisfactory field testing at the research and development stage in ecosystems which could be affected by their use.

The following sequence of steps has emerged in practice:

- laboratory
- greenhouse
- small-scale release with strict containment (not specified in law)
- larger-scale release with more relaxed containment
- placing on the market
- subsequent measures covered by the authorization
- subsequent Member State measures based on safeguard clause

[44] The step-by-step procedure goes back to OECD reports, including OECD, Safety considerations for biotechnology, 1992 (available at www.oecd.org/dataoecd/8/3/2375496.pdf).

The substance of the step-by-step principle was somewhat specified by Commission Guidance which says that "data from each step should be collected as early as possible during the procedure." It points to the possibility that "simulated environmental conditions in a contained system could give results of relevance to deliberate release," such as the simulation of behaviour of microorganisms in the laboratory, and of plants in greenhouses.[45]

The step-by-step principle is an instrument of societal learning. In the initial phase of European genetic engineering legislation, it was at the fore of public debate and became a legal requirement as outlined. With the amendment through Directive 2001/18/EC, monitoring has become an additional instrument. In order to increase safety, and at the same time facilitate the release and market distribution of GMOs, it was emphasized that those issues which, for reasons of time or scale, cannot be solved at one level can be clarified through monitoring at the next level. Monitoring can therefore be seen as a phase of learning following the release or market distribution, respectively. This concerns especially the investigation of effects which cannot be researched on an experimental basis, such as complex interactions on population and ecosystem levels, or cumulative and long-term effects.

As to procedural aspects, the applicant must submit a monitoring plan that contains the following information:[46]

1. methods for tracing the GMOs, and for monitoring their effects;
2. specificity (to identify the GMOs, and to distinguish them from the donor, recipient or, where appropriate, the parental organisms), sensitivity and reliability of the monitoring techniques;
3. techniques for detecting transfer of the donated genetic material to other organisms;
4. duration and frequency of the monitoring.

The monitoring programme is then determined as a condition for the release authorisation. The operator is responsible for implementing the programme and reporting results to the authority.

It is submitted that the step-by-step-principle, including self-monitoring, should also be used in relation to SynBio. Of course, the methodology must still be adapted to the various strands of SynBio and its peculiarities.

Steps in the analysis and assessment of risks

It is characteristic for the risk assessment in form of the environmental risk assessment (ERA) that it processes the data successively in pre-defined steps. The staggered evaluation of risks is finally followed by the risk management, which translates the scientifically informed risk evaluation into measures, i.e. the

[45] Commission Guidance Chap. 3.

[46] Art. 6 (2) (V) and Annex III C of Directive 2001/18/EC.

authorisation, the conditions for the authorisation and, if applicable, the rejection of authorisation.

According to Annex II of Directive 2001/18/EC and the respective Commission Guidance the ERA consists of six steps. Using the language of the Annex the steps can be summarized as follows:

In step 1, the inherent characteristics of the GMO are to be identified. They present factors (or "hazards") that can lead to risks depending on environmental conditions and usage.

In step 2, the potential consequences of each established adverse effect have to be evaluated. The evaluation concerns organisms, populations, species and ecosystems interacting with the GMO. Particular emphasis is given to the expected magnitude of the consequences. The latter can depend on the genetic design, the established adverse effects, the number of released GMOs, the receiving environment, the manner of the release and the control measures taken as well as on a combination of all these factors.

In step 3, the likelihood of the occurrence of each identified potential adverse effect is to be evaluated; here, each effect is examined individually, taking into account the risk factors, the number of released GMOs, the likelihood and frequency of gene transfer, the receiving environment and the conditions of the release.

In step 4, the different magnitudes of consequences (high, moderate, low or negligible) of every risk factor are linked to the different degrees of their likelihood (high, moderate, low or negligible). In addition, the overall uncertainty for each identified risk has to be described, including assumptions and extrapolations made at previous levels in the ERA, different scientific assessments and viewpoints, and the uncertainties contained in each evaluation.

In step 5, management strategies for risks from the deliberate release (or marketing) of GMOs are to be developed. The risk management is to be designed in a way so that identified risks can be controlled and that uncertainties can be covered. Safeguarding measures (coated seeds, isolation distances, etc.) have to be proportionate to the levels of risk and uncertainty.

In step 6, the overall risk of the GMO is determined. This consists of a summary of all identified risks and uncertainties of the examined application, taking into account the magnitude and likelihood of the adverse effects as well as the previous release of other GMOs. The achieved risk reduction caused by the management measures must also be considered.

Core to this 6 step procedure is the distinction between inherent factors of a GMO, adverse effects of these factors through interactions on the levels of the organism, populations, species and ecosystems, the magnitude of each adverse effect, and its likelihood. In addition, the uncertainties of the assessment shall be described. Safeguarding measures shall also be taken into account. This sounds thorough and comprehensive but may not sufficiently reflect the fact that SynBio is too diverse and unstructured to allow for a standardisation of risk assessment. For instance, the fact that much of the produce of SynBio is claimed not to survive under real world conditions must be integrated into the methodology. Likewise, the focus on organisms does not reflect possible risks from bioparts and minimal cells.

Familiarity

The major innovation needed in risk assessment for SynBio will be that the familiarity principle must be modified and finally even abandoned, because the newly designed organisms are intentionally more and more alienated from the genome of existing organisms.

The status of the familiarity principle in the GMO risk assessment can be summarized as follows: Risks to human health and the environment can be caused by traits of the non-modified parental lines and of the genetic modification. The concept of familiarity (or—using about the same approach—comparison with similar organisms or substantial equivalence), which goes back to an OECD paper of 1993, suggests that only effects of the genetic modification should be assessed. This is reasonable; otherwise the applicant could be blamed for adverse effects that are already contained in the parental line. However, critiques have alleged that, by focusing on the modification, the concept of familiarity cuts the organism into pieces and disregards effects of the newly created organism as a whole. Rather than assuming firm knowledge of the unmodified organism, one should rather look for the unexpected, the unfamiliar in interactions between the existing cause-effect network and the newly introduced GM component (Breckling 2004, 52–59).

Asking what the law demands in this regard, it should first of all be noted that the concept of familiarity is not conveyed by the wording of the substantive standard expressed in Directive 2001/18/EC. Rather, Art. 4(1) states comprehensively that the release and the placing on the market of the GMO must not cause any adverse effects. The annexed rules on the ERA, however, state that a comparison with non-modified organisms

> will assist in identifying the particular potential adverse effects arising from the genetic modification. [47]

The new EFSA Guidance of 2010 unwisely reinforces this approach by making the "comparative safety assessment" the core yardstick of risk assessment.[48]

Whether called comparative or not, the examination is not allowed in any case to imply that the transgene has to be considered in isolation. Unintended position effects and mutual reactions at all organismic levels are rather the consequence of genetic modifications and have to be considered to their full extent. Upon closer look this is also envisaged by the EFSA Guidance of 2010. Therefore, the Annex on ERA is still right to regard the comparative approach as a heuristic, rather than constitutive, tool of the risk assessment.

Concerning SynBio, however, even this heuristic function will lose ground with the growing alienation from parental lines of the new synthetic organisms. New methods of risk assessment must be developed. It is suggested that such methodology should start with risk-related analysis of the main strands of developments of

[47] Annex II Directive 2001/18/EC, C.

[48] EFSA Guidance Chap. 2.

this technology. Subcellular parts and protocells, for instance, do not pose a risk of replication and through that of risks attached to life forms, such as becoming dominant in ecosystems. Rather, they are to be evaluated in terms of criteria used for chemicals, such as toxic, carcinogen, mutagen and allergen properties, persistence and bioaccumulation, as well as exposure analysis. Xenobiology is claimed to be safe because resulting organisms can only survive under very artificial circumstances. However, this is not necessarily true, so that scenarios and tests must be developed to prove this assumption. In addition, criteria used for chemicals should be applied. The major challenge will be to develop methods for the vast and ever-expanding works of those kinds of genetic engineering which are increasing the degree of artificiality even more. Specific tests must be developed in order to identify risks. Specific risk abatement technology must also be developed.

As all this costs time and effort, it appears to be advisable to establish a moratorium for the release into the environment of SynBio organisms, as well as a moratorium for the placing on the market of such organisms insofar as this entails any release into the environment.

3 Regulation Ex Post

Regulation ex post makes an actor liable to remedy or compensate for damage he or she has caused. There are various legal bases for such liability, general ones and ones specifically created for GMO-related risks.

The general scheme is tort liability. It presupposes that damage was intentionally or negligently caused to human health or material assets by an operator. The burden of proof, in principle, lies with the victim. Tort liability seldom leads to convictions because the causation and negligence are difficult to prove.

More specific and promising from the victim's perspective is strict liability for GMOs which has been introduced by some countries including Germany. Art. 32 of the German Genetic Engineering Act (Gentechnikgesetz- GentG) provides:

> Where any properties of an organism that result from genetic engineering operations cause the death of a person or injury to his/her health, or damage of property, the operator shall be obliged to give compensation for the damage ensuing therefrom.

No intention or negligence is required. The proof of causation is facilitated in two ways:

Causation from genetic engineering operations is presumed if the damage was caused by genetically modified organisms. The burden of proof that this was not the case lies on the operator.[49]

If the victim brings a prima facie proof that the damage was caused from genetic engineering operations of an operator the operator must disclose

[49] Art. 34 GentG.

information "about the type of and steps involved in the genetic engineering operations performed" by her.[50]

In addition, the liability does not only extend to the victim's own damage but also covers expenditure incurred by her for the restoration of damage to the environment. If, for instance, a bacterium which has been gene-coded for an infectious animal disease, escapes from the laboratory and causes a disease to bees, the operator is liable to pay for the forgone fruit yield and for the restoration of the bee population.

Directive 2004/35[51] establishes a third basis for liability. The concept does not introduce an additional right of a victim against an operator, but empowers and obliges administrative authorities to intervene. This is possible, i.e., if any deliberate release into the environment, transport and market placement of genetically modified organisms causes environmental damage.[52] The administrative authority can order the operator to take remedial action. NGOs are given rights to sue the authority if it remains passive.

Overall, SynBio as far as it is subject to the GMO regime, faces rather strict liability rules. As the special rules all refer to GMOs, they do not apply to technologies or products outside this scope. For this reason it must be considered whether the liability should be extended to those parts of SynBio which do not consist of GMOs in the legal sense, i.e. completely new organisms, organisms whose genome was completely replaced, organisms into which transgenes were inserted by other techniques than those contained in the positive and negative lists, organisms modified by xenobiochemistry, protocells, minimal cells, and bioparts.

4 Conclusion

Other than official statements by governmental and scientific bodies assume[53] the existing regulatory framework cannot be relied on as an adequate means of controlling risks from synthetic biology. Various kinds of SynBio are either not captured by the present regulation, or not appropriately treated by the present risk assessment methodology. This study suggests that the risks from SynBio should carefully and systematically be examined. On such basis new regulation should be introduced. This could be done by extending the scope and improving the risk assessment of the existing regulation on genetically modified organisms, or by taking a new approach that addresses biotechnology in a broad sense, including GMOs, SynBio, new breeding techniques and possibly further variants.

[50] Art. 35 GentG.

[51] Directive 2004/35/CE of the European Parliament and of the Council of 21 April 2004 on environmental liability with regard to the prevention and remedying of environmental damage, OJ L 143, 30.4.2004, p. 56.

[52] Art. 3 para 1 and Annex III of the directive.

[53] See Footnote 13 above.

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