**Technical series on synthetic biology**

**Peer Review**

**European commission comments**

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| **Comments on the Technical Series on Synthetic Biology** |
| **Page #** | **Line #** |  |
| 8 | 1 | General comments that are applicable to the entire report:* Only a fraction of relevant publications are cited throughout the report – many more relevant papers (including more recent ones) have been published in the scientific literature and would be worthwhile citing;
* It may be helpful to clarify the criteria used for selecting, citing or excluding relevant publications;
* A narrative approach is followed to describe some of the relevant information reported in the scientific literature. Yet, the weight of evidence given to the publications cited and statements made therein is not reported, suggesting that each single scientific publication has been attributed an equal weight. However, the quality of scientific publications cited can vary;
* For transparency it would be helpful to “*quote*” the sentences reused/copy pasted from scientific publications;
* In several cases, a single reference is cited to substantiate a statement made in the report, though other publications could be cited in support of that statement;
* Several general statements are made throughout the report, without specifying whether these statements are applicable to all potential SynBio applications or specific ones only. This is confusing, as in many cases, the statements made should not be generalised. It would therefore be helpful to remain as specific as possible and follow a case-specific approach in the report;
* Several of the general statements made are not specific to SynBio applications;
* To focus the report further, perhaps it may be helpful to single out the novel features of SynBio applications as compared with “contemporary” GMOs, and explore the potential challenges they may pose to risk assessment
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| 8 | 18-19 | Could you perhaps be more specific about “(i) contained, industrial, or laboratory settings, (ii) semi-managed, managed, or urban settings, or (iii) unmanaged or wild settings” by providing a short description/explanation in between brackets? |
| 9 | 4 | Delete “the focus on”. |
| 9 | 23 | Replace “issue” with “relevant applications”. |
| 9 | 43-46 | Engineered gene drive applications are also under development to help rescue endangered species. Perhaps this additional type of application could be added to the list |
| 9 | 47 | Delete “such as” (written twice). |
| 10 | 37-39 | In this section, more emphasis could be put on the intended uses of SynBio organisms and their intended outcomes, as these aspects will be key for the identification of plausible pathways to potential harm (idem for section 7 on page 11) |
| 10 | 47 | The terminology “… reach the market” may not be the most appropriate one to use for engineered gene drive applications, as some of these applications may include public or non-commercial use (e.g. philanthropic/charitable purposes). Perhaps alternative wording may be needed for clarity |
| 10 | 47 | The terminology “in a few years” is a bit vague. Can this be made more specific?  |
| 11 | 1-10 | The statements made in section 7 are very general, and may need refinement on a case-by-case basis |
| 11 | 11-26 | A few cases are presented and used to make generalisations for all potential SynBio applications, which may not necessarily be applicable to all such cases in practice. It may be helpful to avoid making generalisations based on a few case studies only.In addition, it is worth noting that most of the considerations in this section are not specific for SynBio. |
| 11 | 30-31 | The statement that “local communities are most likely to be impacted first” is a generalisation that does not apply to all cases, since the impacts and impacted stakeholders will depend on the specific application. We suggest to replace with “local communities may be those to be impacted first”. |
| 11 | 42-43 | It would be helpful to clarify better whether such an engagement is needed for all SynBio applications or specific applications only. Moreover, the need for such engagement should be better explained, and be put in the context of contemporary GMOs (in terms of lessons learnt) |
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| 12 | 23 | Incomplete sentence. |
| 13 | 13 | Replace “impacts” with “products”. Activities and products are regulated, not impacts. |
| 13 | 40 (Table 1) | The terminology “commercially available” may not be the most appropriate one to use for engineered gene drive applications, as some of these applications may include public or non-commercial use (e.g. philanthropic/charitable purposes). Perhaps alternative wording may be needed for clarityIt may be more helpful to present the table in the core text than in the summary of the report, or twice, both in the summary and core text. As stated in the text on page 15 lines 19-23, “the authors recognise that some of the processes or products described in this document may not be considered as synthetic biology approaches and applications by all readers, however the broadest interpretation has been made in order to be as inclusive as possible whilst at the same time not championing this interpretation as being definitive”. Taking into account the definition of synthetic biology, the simple use of genome editing techniques does not make a product a synbio product. In the light of this definition, table 1 presents some applications whose classification under synthetic biology is not justified (e.g. general reference to “genome edited crop plants and farm animals”, in the column on “advanced developments”, and specific reference to “genome edited soya bean and oilseed rape” in the column on “commercially available” applications). We recommend to:1. Replace “genome edited crop plants and farm animals” with “synbio applications of genome edited crop plants and farm animals”.
2. Delete “genome edited soya bean and oilseed rape” from Table 1 and other sections of the document.
3. include the disclaimer above in Table 1 and also in other relevant parts of the document (e.g. page 31, section 3.2.)
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| 15 | 19-23 | As mentioned above, we recommend to include this disclaimer also in Table 1. |
| 19 | 27-28 | Not sure that “circumvent” is the appropriate term to use. Given that gene drives occur naturally in a broad array of organisms, some authors (e.g. Hurst, 2019) have suggested that preferential inheritance may be the rule rather than the exception. Therefore, alternative wording may be helpful.Hurst LD, 2019. A century of bias in genetics and evolution. Heredity, 123, 33–43. |
| 19 | 30 | “… at the expense of their hosts”. Is the spreading always at the cost of their hosts? This may be the case for population suppression strategies/systems but not necessarily for population modification strategies/systems |
| 19 | 37-39 | Perhaps the authors of the report may wish to cite relevant review papers here that provide an overview of the various engineered gene drives developed so far (instead of specific original research papers). Some relevant examples are given for convenience, below.-Champer J, Buchman A and Akbari OS, 2016. Cheating evolution: engineering gene drives to manipulate the fate of wild populations. Nature Reviews Genetics, 17, 146–159.-Hay BA, Oberhofer G and Guo M, 2021. Engineering the composition and fate of wild populations with gene drive. Annual Review of Entomology, 66, 407–434.-Raban RR, Marshall JM and Akbari OS, 2020. Progress towards engineering gene drives for population control. Journal of Experimental Biology, 223, jeb208181. |
| 19 | 39-43 | It would be helpful to consider the publication by Alphey et al. (2020) when addressing the definition and purpose of engineered gene drives. The reference to the publication is given below.Alphey LS, Crisanti A, Randazzo F, et al., 2020. Standardizing the definition of gene drive. PNAS, 117, 30864–30867. |
| 19 | 44-47 | The list of currently proposed and/or developed engineered gene drives is incomplete. Additional designs with different or similar modes of action have been reported in the scientific literature (e.g. home and rescue gene drives, split rescue drive, underdominance gene drives). Perhaps the text could be updated accordingly, or could mention that the field is evolved rapidly and most likely yielding additional new designs and modes of action in the near future. Perhaps the authors of the report may also wish to consider Table 2 of EFSA (2020) for an overview/classification of current engineered gene drives in insects (see also WHO, 2021).-EFSA (European Food Safety Authority), 2020a. Scientific Opinion on the adequacy and sufficiency evaluation of existing EFSA guidelines for the molecular characterisation, environmental risk assessment and post-market environmental monitoring of genetically modified insects containing engineered gene drives. EFSA J. 18, 6297.-WHO (World Health Organization), 2021. Guidance framework for testing genetically modified mosquitoes, second edition. ISBN 978-92-4-002523-3. Available from: <https://www.who.int/publications/i/item/9789240025233> |
| 19 | 44-47 | “…, CRISPR-based homing gene drives are the most adaptable to new species and populations …”. Can a rationale be provided to substantiate/clarify this statement?  |
| 20 | 1-8 | The concept of homing is not explained, though it is a key part of the message to convey. Perhaps a sentence could be added to explain homing |
| 29 | 11 | Would it help to describe the different potential applications first, irrespective of their development status, and then report on their development status (including the Table)? This would enable to provide the full spectrum of potential applications currently proposed (even if hypothetical and only considered through population models), and avoid overlap in some of the subheadings presented (e.g. disease vector control applications: mosquitoes vs. ticks). Once all relevant potential applications have been presented, they could be ranked according to their development status and intended uses. Since the development status of the currently presented applications will evolve (rapidly), it may be more straightforward to describe the potential applications first, and subsequently rank them based on development status. The information provided in the report could easily be reshuffled accordingly. This approach may also ease regular updates of the report in the light of recent and new developments in the field |
| 29 | 31-33 | The criteria used for the categorisation/ranking would benefit from being described in more detail, as this would add clarity and improve understanding. In this respect, there is a need to better to define what is meant with “confined field trials” and list concrete types of field trails that are considered “confined field trials”. The terminology and classification used in the 2021 revised WHO framework for testing GM mosquitoes could be helpful to reproduce here and may ensure the use of standardised/harmonised terminology. WHO (World Health Organization), 2021. Guidance framework for testing genetically modified mosquitoes, second edition. ISBN 978-92-4-002523-3. Available from: <https://www.who.int/publications/i/item/9789240025233> |
| 29 | 35 | For this category the word “commercially available” sounds strange as wild settings are usually managed by governments (as natural parks etc). Also we would expect for this category pro bono, sponsored or academic products. |
| 30 | 27 & 41 | There are different ways to contribute to conservation purposes. Therefore, could different categories of “conservation purposes” be given instead, under an overarching title “conservation purposes. Subheadings could be, for example, “applications for managing “unwanted/harmful/invasive” target species” and “improving the resilience of wild animal and plant populations”? Plus, could examples be given about possible engineered gene drives tailored towards (1) rescuing endangered species and (2) managing invasive species? |
| 31 | 27 | Are the examples given to be considered as deliberate releases into the environment for “commercial” or “experimental” purposes? Would some of the “self-limiting GM insect applications” listed here fall under “advanced development” category instead of “commercially available’?Note also that additional and more recent releases with self-limiting GM insects have been conducted; some of which may be relevant to mention for completeness.Plus, in the case of “self-limiting GM insects”, no distinction is made between “disease vector” and “pest” control purposes, though such a separation is being introduced for engineered gene drive applications (some of which may also be considered as self-limiting GM insects).Note also that some GM insects with engineered gene drives are being designed to be self-limiting and localised. So by default, such systems could also be discussed under the “self-limiting GM insects” heading, so the headings used may benefit from further fune-tuning |
| 32 | 6-8 | Not sure why the term “organisms” is used in the introductory sentences. Perhaps the text could be made more specific by mentioning “disease-spreading mosquitoes” directly.Note also that more recent and relevant publications are available that could be cited here.Connolly JB, Mumford JD, Fuchs S et al (2021) Systematic identification of plausible pathways to harm via problem formulation for investigational releases of a population suppression gene drive to control the human malaria vector *Anopheles gambiae* in West Africa. Malar Journal, doi:10.1186/s12936-021-03674-6  |
| 32 | 16-19 | Is this work to be considered as “research” or “advanced development”? The criteria used for the categorisation could be better clarified to add clarity. Have “confined field trials” been conducted for the application list here?  |
| 32 | 20 | Why are these cases labelled differently than the “self-limiting insects” mentioned earlier in the report? In both cases, “self-limiting insects” are being addressed. Also note that the Oxitec cases mentioned above rely on the fsRIDL technique, so perhaps some alignment is needed to ensure consistency in wording used between both headings.The heading “Genetically engineered bio-containment systems in mosquitoes” is a bit confusing, as self-limiting/localised engineered gene drive systems are under development in insects, including mosquitoes, which would fit under this category too.CRISPR systems for genome engineering can also used to develop GM insect without engineered gene drive(s). Perhaps this point should be made more explicitly throughout the report |
| 38 | 21 | For engineered gene drive applications in insects, perhaps more emphasis should be put on the new modes of action and underlying strategies that are currently proposed and reported in the scientific literature.In this respect, it would be important to mention that recent research efforts aim to develop engineered gene drives that are confinable (i.e. limited in their spread and persistence) and reversible (i.e. recallable from the environment in the event of unwanted consequences). Several approaches have been proposed to restrict the spread of engineered gene drives within a specified target population or geographic region, or to reduce their persistence in target populations over the course of several generation. Likewise, reversal gene drive have been proposed as genetic remediation or neutralising systems that could disable or reverse the effects of a previously released gene drive modified organisms in the event of unintended consequences. Perhaps these developments could be mentioned in the report.Moreover, it may be helpful to indicate that current research efforts also focus on the development of engineered gene drives that are specific, stable and avoid or delay the evolution of resistance against them |
| 41 | 11-12 | There is substantial overlap of information reported in section 4 “Applications of Synthetic Biology and Their Potential Impacts on the Conservation and Sustainable 11 Use of Biological Diversity” and the previous section of the report. To avoid unnecessary duplications, perhaps the intended impacts on ‘wild’ target populations of potential SynBio applications (and thus their intended outcomes) could be merged and addressed in the section C instead of section D. For example, the types of engineered gene drives should be described in section C instead of section D.The potential impacts/risk concerns are addressed in a narrative and non-systematic manner, and tend to be generalisations. Moreover, risk concerns are addressed as plain text without subheadings. For clarity and readability purposes, perhaps it may be helpful to introduce subheadings for relevant groups of risk concerns. For each of these risk concerns perhaps it could be specified whether the risk concerns identified are plausible or not, consequential in terms of harm to human and animal health and the environment, and specific to the case under assessment or not. The lack of efficacy of an engineered gene drive could lead to harm, and thus should be addressed explicitly in the report.Perhaps the authors of the report may wish to follow a more systematic approach for the identification of risk concerns and assess whether they are plausible and consequential. The pathway to potential harm approach could be followed for this purpose. See for example Connolly et al. (2021).Connolly JB, Mumford JD, Fuchs S et al (2021) Systematic identification of plausible pathways to harm via problem formulation for investigational releases of a population suppression gene drive to control the human malaria vector *Anopheles gambiae* in West Africa. Malar Journal, doi:10.1186/s12936-021-03674-6 |
| 41 | 31-32 | The scope of “conservation purposes” should be better defined in the report |
| 41 | 35 | The rationale for focusing on engineered gene drives in this section is not entirely clear, especially in the light of other genetic control approaches that may involve elements of the SynBio toolkit for their engineering/development.Moreover, it seems that the examples given are not all up to date, and that relevant scientific publications, including more recent ones, are not cited. Hence, it would be helpful to cite additional relevant scientific publications, including more recent ones, throughout this section. In this respect, specific emphasis could be given to the revised WHO guidance framework for testing GM mosquitoes.Some of the points raised are not specific to engineered gene drives, and apply to other biological, genetic and chemical disease vector/pest control approaches. Perhaps it would be helpful to focus the text on new or different harms associated with the potential use of engineered gene drives, and distinguish them from similar harms caused by current disease vector/pest control approaches. A way to achieve this is to describe the “novel features” of engineered gene drives as compared with other (current and emerging) disease vector/pest control systems at the beginning of the section to frame the rest of the text better, and enable focusing the text on key differences between engineered gene drive-based systems and other disease vector/pest control ones (see also EFSA GMO Panel, 2020).-EFSA (European Food Safety Authority), 2020a. Scientific Opinion on the adequacy and sufficiency evaluation of existing EFSA guidelines for the molecular characterisation, environmental risk assessment and post-market environmental monitoring of genetically modified insects containing engineered gene drives. EFSA J. 18, 6297.-WHO (World Health Organization), 2021. Guidance framework for testing genetically modified mosquitoes, second edition. ISBN 978-92-4-002523-3. Available from: <https://www.who.int/publications/i/item/9789240025233> |
| 41 | 36-37 | Not all the intended uses listed here are specific to GM insects with engineered gene drives. Other (novel) genetic control approaches have more or less similar goals. Perhaps this point could be acknowledged more explicitly  |
| 41 | 38-39 | What about the potential to help rescue endangered species? |
| 42 | 20-24 | Off-target mutations do not constitute *per se* an unwanted impact on biodiversity. We suggest to delete “off-target mutations”. To consider possible impacts of off-target mutations, we suggest to amend the beginning of the sentence as follows: “Further, depending on the type and scale of the intended and unintended modifications,…” |
| 43 | 32-45 | The text does not explore how loss of engineered gene drive efficacy could result in harm. Perhaps this requires further consideration. Moreover, it would be helpful to mention to which extent the potential for resistance to evolve is higher, similar or lower for engineered gene drive systems compared to other disease vector/pest control systems |
| 44 | 1-10 | The points raised are not specific to engineered gene drives, but also apply to other disease vector/pest control strategies. It would therefore be important to underline more explicitly what novel features of engineered gene drives may cause more or different harms compared to currently used control systems  |
| 44 | 11-24 | It may be helpful to address the potential spread and persistence characteristics of engineered gene drives at the beginning of the section instead of at the end |
| 44 | 35-40 | Several impacts mentioned in this paragraph have been considered, but not really observed from analogous applications exploiting genetic modification technology in agriculture. We suggest to replace “observed” with “considered”. |
| 44 | 41-46 | As reported later in the text, “mutagenesis techniques used in conventional breeding are rife with off-target effects…” (page 45, lines 6-7). Therefore, we suggest to amend the text here as follows: “again, phenomena that have been reported with classical genetic engineering as well as conventional breeding”. |
| 45 | 9 | We believe that an important consideration has not been reported in the document and we suggest to include the following: “Experimental evidence indicates that off-target mutations potentially induced by genome editing techniques are of the same type as those mutations obtained through conventional breeding (EFSA Panel on Genetically Modified Organisms (GMO), ‘Applicability of the EFSA Opinion on SDNs type 3 for the safety assessment of plants developed using SDNs type 1 and 2 and oligonucleotide-directed mutagenesis’, EFSA Journal 2020;18(11):6299. doi:10.2903/j.efsa.2020.6299). |
| 45 | 11-13 | We believe that the sentence, as it is formulated, does not reflect fully the statement of the European Commission High Level Group of Scientific Advisors 2017.We suggest to amend the sentence as follows: “ Those off-target changes that remain may or may not lead to phenotypic effects…” |
| 50 | 29-32 | The statement is not applicable to all engineered gene drive approaches (e.g. self-limiting/localised systems) and should be revised |
| 56 | 1-8 | The flow of arguments given is challenging to follow/grasp. Plus, some of the statements made a rather vague/cryptic “different methods and techniques of synthetic biology may need different forms and levels of oversight” and thus not helpful |
| 56 | 45 | General comment on 6.1:This section should be improved and become more factual. The section focuses only on gene drives, genome editing and RNA-based technologies and lacks any consideration on other Synbio applications that are relevant within this context. Please note that the two recent EFSA opinions  on synthetic biology plants (<https://www.efsa.europa.eu/en/efsajournal/pub/6301>) and microorganisms (<https://www.efsa.europa.eu/en/efsajournal/pub/6263>) cover a wider range of synbio products. The ones of microorganisms also include metabolic engineering and xenobionts. The practical examples there demonstrate more systematically and in detail the adequacy of risk assessment methodologies. We therefore recommend to expand the scope of section 6.1 to cover other relevant Synbio areas (e.g. xenobiology). |
| 57 | 14-16 | It may be helpful to summarise these “novel risks” and “high levels of uncertainty” somewhere in the report (perhaps in a table), and compare them with relevant comparators (including systems). Moreover, this statement may not be applicable to all potential SynBio applications, so may benefit from being nuanced. Also the statement that these applications are challenging existing regulatory systems in an unprecedented fashion is very general and, as such, not supported by evidence. |
| 57 | 20-25 | The flow of arguments is challenging to follow. Moreover, the authors may wish to expand on the fact risks/potential for harm can be assessed in a relative (comparative) manner (and thus against an acceptable baseline) or in an absolute manner. The report tends to focus on the absolute risks, without addressing relative risk assessments |
| 57 | 46 | The quality of this section could be further improved.  |
| 57 | 4-6 | We propose to replace ‘new risk assessment’ by ‘new risk assessment framework’. |
| 57 | 12-13 | ‘The process should include mechanisms that facilitate the effective engagement of stakeholders and help integrate these considerations within the overall decision-making process’ This would benefit from concrete examples where it has been successfully accomplished.  |
| 57 | 30 | Case. Add “case and its intended use” |
| 57 | 38 | Based in science, add “and based on scientific evidence that is available.” |
| 58 | 9 | Irreversibility is not applicable to all engineered gene drive applications, so this points needs to be nuanced. Moreover, irreversibility is likely to pose challenges for risk managers and decision makers but not necessarily risk assessors |
| 58 | 10-12 | And what about spatial and temporal scale of spread of some gene drive modified organisms? |
| 58 | 16-17 | It depends on the engineered gene drive systems so once again this statement should be nuanced |
| 58 | 20 | Please correct the reference “ Naegeli et al., 2020” as follows “EFSA GMO Panel, 2020” |
| 58 | 33-43 | Once more, very general statements that may not be applicable to all potential engineered gene drive applications |
| 58 | 37 | Models are not only used for prediction purposes, but also to better understand the system under assessment |
| 58 | 38 | What about self-limiting/localised engineered gene drives? |
| 58 | 42-43 | This statement is too general to be helpful – further ecological work on what, and for what purpose?  |
| 59 | 13 | Reference to Court of Justice of the EU, 2018 is not related to the context. |
| 59 | 29 | Add citation for EFSA GMO Panel opinion on SDN 1, 2 and ODM. Not in reference list or in the text. |
| 59 | 7-8 | Proposed citation to add/consider: EFSA GMO panel scientific opinion on SynBio plants discusses the potential off target effect in genome edited synbio plants, based on case studies.  |
| 59 | 25-41 | Parties may also have specific guidance. Consider to add the references, differentiating the levels of data requirements.  |
| 60 | Line 7; Section 6.1.3 | EFSA GMO panel has published in 2017 a guiding note on the assessment of RNAi off targets in plants and a review of it’s activities (including several scientific opinions) on the risk assessment of GM plants based on RNAi. This recent work could be cited in this section, with reference to the EFSA scientific opinions for recently commercialized maize and soybean GM plants, as well as the external reports reviewing the state of the art for MC, FF, ERA (Paces 2017, Davalos 2019 and Christeans 2018) |
| 60 | 3 | Only a fraction of relevant publications are cited – many more relevant papers (including more recent ones) have been published in the scientific literature |
| 61 | 29 | Post-release/market environmental monitoring could be addressed as additional risk management strategy |
| 64 | 30-31 | The potential of the method cited here is controversial. The European Network of GMO Laboratories (ENGL, 2/10/2020) concluded that “as the method thus does not allow to distinguish single nucleotide variants generated by genome editing from those obtained with classical breeding techniques or by natural mutation, it cannot be applied for unequivocal detection, identification and quantification”. The ENGL also concluded that “additional validation work would be required to evaluate further the specificity, sensitivity and applicability of the method”. We recommend to include these conclusions in the text. |
| 64 | 36 | We suggest to include an important conclusion of the European Network of GMO Laboratories, 2019: “Validation of an event-specific detection method and its implementation for market control is only feasible for genome-edited plant products carrying a known DNA alteration that has been shown to be unique”. |
| 66 | 15-16 | The exemptions are not always treated as conventional products. Therefore, it would be more accurate to say that some countries treat the exemptions as conventional products while others apply specific conditions such as making a public consultation, publishing those decisions or introducing the exemptions in specific registers, requiring specific follow up or monitoring reports. |
| 66 | 38-40 | The European Court of Justice ruled that organisms obtained by mutagenesis are GMOs as defined in EU legislation and that new mutagenesis techniques are subject to the obligations of the EU GMOs legislation (Court of Justice of the European Union Case C-528/16[[1]](#footnote-2)).  |
| 70 | Line 12 | That that (remove repeated word) |
| 107 | 36 | Please correct the reference “ Naegeli et al., 2020” as follows “EFSA GMO Panel, 2020” |
| 165 | 20-26 | Please correct the reference as follows: “EFSA GMO Panel (EFSA Panel on Genetically Modified Organisms), Naegeli, H, Bresson, J-L, Dalmay, T, Dewhurst, IC, Epstein, MM, Guerche, P, Hejatko, J, Moreno, FJ, Mullins, E, Nogué, F, Rostoks, N, Sánchez Serrano, JJ, Savoini, G, Veromann, E, Veronesi, F, Bonsall, MB, Mumford, J, Wimmer, EA, Devos, Y, Paraskevopoulos, K and Firbank, LG, 2020. Scientific Opinion on the adequacy and sufficiency evaluation of existing EFSA guidelines for the molecular characterisation, environmental risk assessment and post-market environmental monitoring of genetically modified insects containing engineered gene drives. *EFSA Journal* 2020;18(11):6297, 90 pp. <https://doi.org/10.2903/j.efsa.2020.6297>” |

Please submit your comments to secretariat@cbd.int.

1. Court of Justice of the European Union. (2018). Judgment Of the Court (Grand Chamber): Mutagenesis 40 — Directive 2001/18/EC, Interpretation and assessment of validity — Notion of ‘genetically 41 modified organism’ — Common catalogue of varieties of agricultural plant species — New 42 techniques of mutagenesis. [http://curia.europa.eu/juris/documents.jsf?num=C-528/16#](http://curia.europa.eu/juris/documents.jsf?num=C-528/16) [↑](#footnote-ref-2)