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Stakeholder questionnaire on new genomic techniques to contribute to a Commission study requested by the Council

Fields marked with * are mandatory.

Questionnaire on new genomic techniques to contribute to the study requested by the Council

Discussed and finalised in the Ad-hoc Stakeholder meeting on 10 February 2020

Background

The Council has requested [1] the Commission to submit, by 30 April 2021, "a study in light of the Court of Justice's judgment in Case C-528/16 regarding the status of novel genomic techniques under Union law" (*i.e.* Directive 2001/18/EC, Regulation (EC) 1829/2003, Regulation (EC) 1830/2003 and Directive 2009/41/EC).

To respond to this Council's request, the Commission is collecting contributions from the stakeholders through the questionnaire below. The study covers all new genomic techniques that have been developed after 2001.

Instructions

For the purpose of the study, the following definition for new genomic techniques (NGTs) is used: techniques that are capable of altering the genetic material of an organism and which have emerged or have been developed since 2001 [2].

Unless specified otherwise, the term "NGT-products" used in the questionnaire covers plants, animals, micro-organisms and derived food and feed products obtained by NGTs for agri-food, medicinal and industrial applications and for research.

Please substantiate your replies with explanations, data and source of information as well as with practical examples, whenever possible. If a reply to a specific question only applies to specific NGTs/organisms, please indicate this in the reply.

Please indicate which information should be treated as confidential in order to protect the commercial

interests of a natural or legal person. Personal data, if any, will be protected pursuant to Regulation (EU) 2018/1725 [3].

[1] Council Decision (EU) 2019/1904, OJ L 293 14.11.2019, p. 103-104, https://eur-lex.europa.eu/eli/dec/2019/1904/oj
[2] Examples of techniques include: 1) Genome editing techniques such as CRISPR, TALEN, Zinc-finger nucleases, mega nucleases techniques, prime editing etc. These techniques can lead to mutagenesis and some of them also to cisgenesis, intragenesis or transgenesis. 2) Mutagenesis techniques such as oligonucleotide directed mutagenesis (ODM). 3) Epigenetic techniques such RdDM. Conversely, techniques already in use prior to 2001, such as Agrobacterium mediated techniques or gene gun, are not considered NGTs.
[3] Regulation (EU) 2018/1725 of the European Parliament and of the Council of 23 October 2018 on the protection of natural persons with regard to the processing of personal data by the Union institutions, bodies, offices and agencies and on the free movement of such data, and repealing Regulation (EC) No 45/2001 and Decision No 1247/2002/EC, OJ L 295, 21.11.2018, p. 39–98

Guidelines

Please note that the survey accepts a maximum of 5000 characters (with spaces) per reply field. You might be able to type more than 5000 characters, but then the text will not be accepted when you submit the questionnaire. You will also receive a warning message in red colour below the affected field.

You have the option to upload supporting documentation in the end of each section. You can upload multiple files, up to the size of 1 MB. However, note that any uploaded document cannot substitute your replies, which must still be given in a complete manner within the reply fields allocated for each question.

You can share the link from the invitation email with another colleague if you want to split the filling-out process or contribute from different locations; however, remember that all contributions feed into the same single questionnaire.

You can save the draft questionnaire and edit it before the final submission.

You can find additional information and help here: https://ec.europa.eu/eusurvey/home/helpparticipants

Participants have until 15 May 2020 (close of business) to submit the questionnaire via EUsurvey.

QUESTIONNAIRE

Please provide the full name and acronym of the EU-level association that you are representing, as well as your Transparency Registry number (if you are registered)

If the name of the association is not in English, please provide an English translation in a parenthesis

European Academies' Science Advisory Council (EASAC)

Please mention the sectors of activity/fields of interest of your association

EASAC covers all scientific and technical disciplines, with a focus on biosciences, environment and energy (https://easac.eu/). Work on NRTs falls into EASAC's Biosciences Programme (https://easac.eu/programmes/biosciences/). With regards to NRTs, the EU national academies of science, who are members of EASAC, may fund or otherwise support activities involved in R&D of NGTs. Many scientists who are Fellows of national academies will be working on R&D of NGTs. However, this consultation response focuses only on EASAC's published work to provide evidence and advice to policy makers about NGTs and we do not directly discuss R&D conducted by member academies and their Fellows. Furthermore, although EASAC's work has previously covered all applications of NGTs (with a focus on genome editing), for the purposes of the present consultation we confine ourselves to applications associated with new plant breeding techniques. In consequence, we make no response to questions 2 and 4-8 as these are not applicable within the terms of our defined remit for this consultation. Our responses to the individual questions draw on recent publications by EASAC, which will be cited.

If applicable, please indicate which member associations (national or EU-level), or individual companies /other entities have contributed to this questionnaire

EASAC provides a means for the national science academies of the EU Member States (together with Norway, Switzerland and the UK) to collaborate with each other in giving advice to European policy makers. The EASAC publications we cite are consensus documents, approved after review by all member academies. This consultation response was discussed in draft with members of the EASAC Biosciences Steering Panel (https://easac.eu/programmes/biosciences/steering-panel-members/), who have the responsibility to advise on the EASAC Biosciences Programme.

If applicable, indicate if all the replies refer to a specific technique or a specific organism

EASAC's previous work has focused on crop plants and, primarily, on genome editing.

A - Implementation and enforcement of the GMO legislation with regard to new genomic techniques (NGTs)

* **1. Are your members developing, using, or planning to use NGTs/NGT-products?**

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please provide details

EASAC's member academies and their Fellows have R&D experience with NGTs. Our EASAC consultation response does not discuss directly the detail of these activities but, rather, draws on our previously published, science-based consensus advice to policy makers.

* **2. Have your members taken or planned to take measures to protect themselves from unintentional use of NGT-products?**

- ( ) Yes
- ( ) No

- [x] Not applicable

*** 3. Are you aware of initiatives in your sector to develop, use, or of plans to use NGTs/NGT-products?**

- [x] Yes
- [ ] No
- [ ] Not applicable

* Please provide details

From our expert discussions we are aware of scientific literature describing the use of genome editing for new plant breeding techniques, e.g. to develop varieties more resistant to abiotic and biotic stresses and to improve the nutritional value of crops. A general discussion of the issues is in EASAC's 2020 Commentary 'The regulation of genome-edited plants in the European Union' (https://easac.eu/publications/details/the-regulation-of-genome-edited-plants-in-the-european-union/). Marketed and other examples of NGT-products are discussed in further detail in the 2019 joint Statement by the German National Academy of Sciences Leopoldina, the Union of the German Academies of Sciences and Humanities, and the German Research Foundation 'Towards a scientifically justified, differentiated regulation of genome edited plants in the EU' (https://www.leopoldina.org/en/publications/detailview/publication/wege-zu-einer-wissenschaftlich-begruendeten-differenzierten-regulierung-genomeditierter-pflanzen-in/). For further recent scientific literature on products and technologies, see for example, Schiemann et al. (2019), Bailey-Serres et al. (2019), Quaim (2020), and the sources cited in the Statement by the Group of Chief Scientific Advisors of the European Commission, 'A scientific perspective on the regulatory status of products derived from gene editing and the implications for the GMO Directive' (https://op.europa.eu/en/publication-detail/-/publication/a9100d3c-4930-11e9-a8ed-01aa75ed71a1/language-en/format-PDF/source-94584603).

Schiemann et al. (2019) Risk assessment and regulation of plants modified by modern biotechniques: current status and future challenges. Annual Review of Plant Biology 70, 699-726. https://doi.org/10.1146/annurev-arplant-050718-100025
Bailey-Serres et al. (2019) Genetic strategies for improving crop yields. Nature 575, 109-118. https://doi.org/10.1038/s41586-019-1679-0
Qaim (2020) Role of new plant breeding technologies for food security and sustainable agricultural development. Applied Economic Perspectives and Policy. https://doi.org/10.1002/aepp.13044

*** 4. Do you know of any initiatives in your sector to guard against unintentional use of NGT-products?**

- [ ] Yes
- [ ] No
- [x] Not applicable

*** 5. Are your members taking specific measures to comply with the GMO legislation as regards organisms obtained by NGTs?**

Please also see question 8 specifically on labelling

- [ ] Yes
- [ ] No
- [x] Not applicable

*** 6. Has your organisation/your members been adequately supported by national and European authorities to conform to the legislation?**

- [ ] Yes
- [ ] No

- (●) Not applicable

* **7. Does your sector have experience or knowledge on traceability strategies, which could be used for tracing NGT-products?**
  - ( ) Yes
  - ( ) No
  - (●) Not applicable

* **8. Are your members taking specific measures for NGT-products to ensure the compliance with the labelling requirements of the GMO legislation?**
  - ( ) Yes
  - ( ) No
  - (●) Not applicable

* Please describe the measures and their effectiveness including details on the required financial, human resources and technical expertise

Not applicable within the terms of our defined remit for this consultation response

* What best practices can you share?

Not applicable within the terms of our defined remit for this consultation response

* 8 bis. What challenges have you encountered?

Not applicable within the terms of our defined remit for this consultation response

* **9. Do you have other experience or knowledge that you can share on the application of the GMO legislation, including experimental releases (such as field trials or clinical trials), concerning NGTs/NGT-products ?**
  - (●) Yes
  - ( ) No
  - ( ) Not applicable

* Please describe for the:
  - [x] Agri-food sector
  - [ ] Industrial sector
  - [ ] Medicinal sector

Agri-food sector

Yes, for the agri-food sector, we have previously expressed concerns about the difficulty in conducting secure field trials in some Member States, see the EASAC and German Academies' reports cited in the answer to Q 3. We have also previously expressed concern about the implications of GMO legislation in deterring academic research in all the plant sciences, including fundamental research, see EASAC's 2020 Commentary 'The regulation of genome-edited plants in the European Union' (https://easac.eu/publications/details/the-regulation-of-genome-edited-plants-in-the-european-union/) and the answer to Q 12.

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B - Information on research on NGTs/NGT-products

* **10. Are your members carrying out NGT-related research in your sector?**

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please specify including subject, type of research, resources allocated, research location

As described in the answer to Q1, many EASAC member academies and their Fellows and scientists are active in NGT-related research. However, in its policy advisory work, EASAC has not conducted comprehensive assessment or auditing of these many activities.

* **11. Are you aware of other NGT-related research in your sector?**

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please specify

Yes, as described in the answer to Q 3.

* **12. Has there been any immediate impact on NGT-related research in your sector following the Court of Justice of the EU ruling on mutagenesis?**

Court of Justice ruling: Case C-528/16 http://curia.europa.eu/juris/documents.jsf?num=C-528/16

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please describe

It is still relatively early to quantify the negative impact on R&D or to differentiate specific, immediate effects of the ECJ ruling from the sustained impacts incurred during the long history of over-regulation of plant biotechnology in the EU (leading for example, to movement of field studies to outside the EU). However, there is some evidence for negative impacts on science, e.g. discussed by Wight (2018) and Wasmer (2019). Negative effects on SMEs are discussed in the Statement of the Group of Chief Scientific Advisors cited in the answer to Q 3. A survey of Dutch plant breeders showed a majority agreeing with the statement "The decision of the EU Court of Justice has a negative impact on the investment in CRISPR-Cas technology in the company" (Wesseler et al. (2019). There is also evidence for Europe falling behind in patenting genome editing-based plant biotechnology, see Martin-Laffon et al. (2019).

Wight (2018) Strict EU ruling on gene-edited crops squeezes science. Nature 563, 15-16. https://www.nature.com/articles/d41586-018-07166-7
Wasmer (2019) Roads forward for European GMO policy – uncertainties in wake of ECJ judgement have to be mitigated by regulatory reform" Frontiers in Bioengineering and Biotechnology. https://doi.org/10.3389/fbioe.2019.00132
Wesseler (2019) The economics of regulating new plant breeding technologies – implications for the bioeconomy illustrated by a survey among Dutch plant breeders", Frontiers in Plant Science 10, https://doi.org/10.3389/fpls.2019.01597
Martin-Laffon et al. (2019) "Worldwide CRISPR patent landscape shows strong geographical bias" Nature Biotechnology 2019 37, 613-620). https://doi.org/10.1038/s41587-019-0138-7

*** 13. Could NGT-related research bring benefits/opportunities to your sector/field of interest?**

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please provide concrete examples/data

Yes, as described partly in answer to Q 3. NGT-research is, of course, important in terms of generating improved products (see answer to Q 16) and also, for example, for building research competencies in functional genomics, training the next generation of skilled researchers and developing new partnerships. There are also considerable opportunities for developing new tools and exploring new applications, for example:

1. To accelerate the domestication of semi-domesticated or even wild plants, see Østerberg et al. (2017).
2. In addition to generating potential benefits for food and nutrition security, use of NGTs in plants can be expected to modify and improve biosynthetic pathways in pursuit of objectives for the Bioeconomy. For example, the biosynthesis of medicinal products, other high-value chemicals and the building blocks for renewable industrial synthesis. See, for example, Tatsis and O'Connor (2016), and Najera et al. (2019).

Østerberg et al. (2017) Accelerating the domestication of new crops: feasibility and approaches" Trends in Plant Science 22, 373-384. https://doi.org/10.1016/j.tplants.2017.01.004
Tatsis and O'Connor (2016) New developments in engineering plant metabolic pathways. Current Opinion in Biotechnology 42, 126-132. https://doi.org/10.1016/j.copbio.2016.04.012
Mortimer (2019) Plant synthetic biology could drive a revolution in biofuels and medicine. Experimental Biology and Medicine 244, 323-331. https://doi.org/10.1177%2F1535370218793890
Najera et al. (2019) Application of multiplex genome editing in plants. Current Opinion in Biotechnology 59, 93-102. https://doi.org/10.1016/j.copbio.2019.02.015

*** 14. Is NGT-related research facing challenges in your sector/field of interest?**

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please provide concrete examples/data

Yes. There are many new research opportunities coming within range but EU competitiveness depends on the research funding available, human resources, and the capacity of innovative companies to develop crops with new and improved traits. Thus, as described in the sources cited in the answer to Q 3, a major challenge is the legacy of bureaucratic, inflexible regulation of GMOs compounded by the recent ECJ ruling. As noted in previous answers, this will increase the obstacles for academic and industry researchers. It is acknowledged that these issues are controversial and, therefore, a further, continuing challenge for researchers is to engage with all stakeholders to discuss the controversies and to try to resolve differing perspectives by sharing robust scientific evidence.

*** 15. Have you identified any NGT-related research needs/gaps?**

- (●) Yes
- ( ) No
- ( ) Not applicable

* Please specify which needs/gaps, explain the reasoning and how these needs/gaps could be addressed

Yes, gaps have been identified and discussed in the sources cited in the answer to Q 3. Gaps extend across the spectrum of R&D: from the essential commitment to invest in basic research, which provides the resource for all subsequent applications, through to investment in field trials providing proof-of-principle under realistic conditions. There must also be public funding for research on the ethical and societal consequences of products and application scenarios of NGTs.

However, it is insufficient to address research needs without also addressing the regulatory impediments to using the research outputs for innovative products and practices: there is currently a policy disconnect between supporting and using research. EU citizens are poorly served if their contribution to the funding for cutting edge science does not lead to them benefitting from the knowledge generated.

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C - Information on potential opportunities and benefits of NGTs/NGT-products

*** 16. Could NGTs/NGT-products bring benefits/opportunities to your sector/field of interest?**

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

Yes, although it is still early in the application of NGTs we anticipate that there will be continuing opportunities to develop improved crops for Europe and worldwide use. Some examples are provided in the sources cited in Qs 3 and 13 and in the Statements by the Group of Chief Scientific Advisors and by the German Academies (who also cross-reference the work by IPCC to demonstrate potential benefits). In addition, the reports by the InterAcademy Partnership on food and nutrition security (Opportunities for future research and innovation on food and nutrition security and agriculture; https://easac.eu/publications/details/opportunities-for-future-research-and-innovation-on-food-and-nutrition-security-and-agriculture/) and by EASAC on the impacts of climate change on health (The imperative of climate action to protect human health in Europe; https://easac.eu/publications/details/the-imperative-of-climate-action-to-protect-human-health-in-europe/) discuss how NGTs may prove valuable in helping to develop climate-resilient agriculture.

* Are these benefits/opportunities specific to NGTs/NGT-products?

- (●) Yes
- ( ) No

* Please explain

We have not assessed benefits in terms of particular stakeholders e.g. farmers, plant breeders, food processors, and retailers because our focus is more broadly on the societal benefits for food and nutrition security. In many cases, the benefits achieved may be specific for NGTs insofar as they cannot be readily achieved presently by other approaches available.

We emphasise that NGTs are a promising tool to achieve sustainable agriculture and that they must be used together with other tools as part of the deployment of all available approaches to achieve food and nutrition security and build on existing good agronomic practice. We also emphasise that setting priorities for sustainable agricultural production must be part of an integrative food systems approach, taking account of the availability of other critical natural resources and encompassing both supply-side and demand-side issues: reducing food waste and changing to healthier consumption patterns.

There is no time to lose in resolving the problems for food and nutrition security, and the potential costs of not using a new technology or being slow in adoption must be acknowledged. The production of more food, more sustainably, requires the development of crops that can make better use of limited resources and will contribute significantly to attaining multiple Sustainable Development goals (SDGs).

* **17. Could NGTs/NGT-products bring benefits/opportunities to society in general such as for the environment, human, animal and plant health, consumers, animal welfare, as well as social and economic benefits?**

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

Yes as noted in our answer to Q 16, and when NGTs/NGT-products are used as part of the deployment of all available tools to increase food and nutrition security. EASAC's work focuses on key issues for society and we discuss the importance of promoting both human health and planetary health (including animal health) in EASAC's 2019 report 'The imperative of climate action to protect human health in Europe (https://easac.eu/publications/details/the-imperative-of-climate-action-to-protect-human-health-in-europe/). In addition, in the context of achieving the SDGs, we discuss integration of societal benefits across multiple sectors, in the 2017 report 'The regulation of genome-edited plants in the European Union' (https://easac.eu/publications/details/genome-editing-scientific-opportunities-public-interests-and-policy-options-in-the-eu/).

One example of what is already possible is provided by a commercialised "high oleic" soybean oil engineered to have greater stability and no trans-fat. This gene-edited product is now available in the USA for restaurant use (Wilke (2019) Gene-edited soybean oil makes restaurant debut. The Scientist 12 March 2019. https://www.the-scientist.com/news-opinion/gene-edited-soybean-oil-makes-restaurant-debut-65590).

* Under which conditions do you consider this would be the case?

Capitalising on NGT opportunities will be likely to advance multiple EU goals, especially for the European Green Deal, the "Farm to Fork" strategy, the Common Agricultural Policy, and the Bioeconomy. If the NGT opportunities are not realised, then European agriculture will become less and less competitive and Europe will have to import an increasingly greater proportion of its food and feed, which will increasingly be produced using NGTs outside the EU. Another consequence of not using NGTs for agriculture is that the EU will continue to export its lack of environmental sustainability to the rest of the world, as a result of its inefficient use of land and other natural resources.

In general, we would like to express the concern that this consultation is too insular in its focus on the EU consequences for NGT-products. EU policy makers must pay more attention to the wider international consequences of their domestic policy choices. In our previous EASAC report 'Planting the future: opportunities and challenges for using crop genetic improvement technologies for sustainable agriculture' (https://easac.eu/publications/details/planting-the-future-opportunities-and-challenges-for-using-crop-genetic-improvement-technologies-for-sustainable-agriculture/) we have commented on, for example, the negative consequences for African countries arising from EU GMO policy and the contradiction between these consequences and the desired objectives of EU international R&D collaborations. Another recent example for lack of European consideration of the wider consequences of EU policy choices is provided by the disconnect between the European Commission-supported encouragement of skills and research for next generation genomics for crops in India (AdaptNET workshop 'Strengthening education, research and innovation for climate smart crops in India', https://www.adaptnet.aua.gr/index.php/events-adaptnet/5-workshop-4) and the likely deterrent effect of EU NGT regulation on Indian exports to the EU.

* Are these benefits/opportunities specific to NGTs/NGT-products?

- (●) Yes
- ( ) No

* Please explain

In many cases, the benefits achieved may be specific for NGTs insofar as they cannot be readily achieved presently by other approaches available.

*

18. Do you see particular opportunities for SMEs/small scale operators to access markets with their NGTs/NGT-products?

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

One problem for EU SMEs is that they cannot afford the high costs of lengthy investment required for R&D and commercialisation of new crops that is occasioned by the inflexible regulatory demands. If the regulatory framework was reformed to be evidence-based and proportionate, then there would be many new opportunities for SMEs – and this would also lead to a challenging of the monopoly position currently held by major multi-national companies. It is also important to realise that SMEs and researchers in developing countries would benefit from EU regulatory reform encouraging their, as well as EU, innovation.

*** 19. Do you see benefits/opportunities from patenting or accessing patented NGTs/NGT-products?**

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

Issues for patenting are discussed in detail in the Statement by the German Academies, 'Towards a scientifically justified, differentiated regulation of genome edited plants in the EU' (https://www.leopoldina.org/en/publications/detailview/publication/wege-zu-einer-wissenschaftlich-begruendeten-differenzierten-regulierung-genomeditierter-pflanzen-in/). We make one additional point now: protection of intellectual property rights is important but competition might be enhanced by further exploration of the options for maintaining co-existence between breeder's rights and patents. Plant Breeder's Rights provides a well-tried and tested system whereby breeders can secure financial returns on the release of a successful variety without jeopardising future benefits to be derived by even further genetic improvement that might be achieved by others (see EASAC's 2020 Commentary 'The regulation of genome-edited plants in the European Union'; https://easac.eu/publications/details/the-regulation-of-genome-edited-plants-in-the-european-union/)

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eeb68964-ca80-4428-9e3b-ddcc06b8315a/EASAC_Planting_the_Future_Q17.pdf
0637f4a5-4a7f-4a25-a69a-765644cc75ab/EASAC_Report_Genome_Editing-Q17.pdf

D - Information on potential challenges and concerns on NGTs/NGT-products

*** 20. Could NGTs/NGT-products raise challenges/concerns for your sector/field of interest?**

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

Yes, as described in the previous answers.

* Are these challenges/concerns specific to NGTs/NGT-products?

- ○ Yes
- ◉ No

* Please explain why not

No, the concerns that are expressed are not specific to NGTs. We emphasise the point that all innovative products in this sector – or any other sector – must be appropriately assessed by evidence-based procedures for risk and benefit, irrespective of the method of production. In our view, a significant legitimate concern is that, if the product cannot be developed in the EU, then the sector will migrate to outside the EU.

* **21. Could NGTs/NGT-products raise challenges/concerns for society in general such as for the environment, human, animal and plant health, consumers, animal welfare, as well as social and economic challenges?**

- ◉ Yes
- ○ No

* Please describe and provide concrete examples/data

Yes, it is well-known that many stakeholders think concerns are appropriate. The evidence for safety of GMOs has been collated by the European Commission and extensively discussed elsewhere, including in the EASAC reports and the Statement by the German Academies previously cited. The published literature continues to substantiate the safety of GMO crops after decades of testing of food and feed products – the technology used to produce them is not inherently hazardous. See, for example, Delaney et al. (2018) and Lassoued et al. (2019). It should also be appreciated that other, less selective, mutagenesis techniques (such as radiation-induced) have been used for decades, without GMO-specific regulation. As Qaim (2020) notes “Based on the scientific evidence available there is no justification to regulate GMOs differently from conventionally bred crops” and there is no reason to suppose that the more precise gene editing techniques add new risks.
It is vital to use the best scientific evidence in all discussions and in challenging assumptions. For example, a case can be made that NGTs are not incompatible with organic farming (see, for example, Marchman Andersen et al. (2015).

In our view, the EU should seek to regulate the trait and/or product rather than the technology used in generating that product. That is, when considering safety issues, the focus should be on assessing the novel attributes of the plant that might represent a risk to the environment or human health, irrespective of the breeding technique employed.

Delaney et al. (2018) Food and feed safety of genetically engineered food crops. Toxicological Sciences 162, 361-371. https://doi.org/10.1093/toxsci/kfx249
Lassoued et al. (2019) Risk and safety considerations of genome edited crops: expert opinion. Current Research in Biotechnology 1, 11-21. https://doi.org/10.1016/j.crbiot.2019.08.001.
Qaim (2020) Role of new plant breeding technologies for food security and sustainable agricultural development. Applied Economic Perspectives and Policy. https://doi.org/10.1002/aepp.13044
Marchman Andersen et al. (2015) Feasibility of new breeding techniques for organic farming. Trends in Plant Science 20, 426-434. https://doi.org/10.1016/j.tplants.2015.04.011

* Under which conditions do you consider this would be the case?

We do not have anything further to add to our previous answers.

* Are these challenges/concerns specific to NGTs/products obtained by NGTs?

- (●) Yes
- ( ) No

* Please explain

We do not have anything further to add to our previous answers.

* **22. Do you see particular challenges for SMEs/small scale operators to access markets with their NGTs /NGT-products?**

- (●) Yes
- ( ) No

* Please explain and provide concrete examples and data

Yes, as described in the answer to Q 18.

* **23. Do you see challenges/concerns from patenting or accessing patented NGTs/NGT-products?**

- (●) Yes
- ( ) No

* Please describe and provide concrete examples/data

See answer to Q 19

Please upload any supporting documentation for this section here. For each document, please indicate which question it is complementing

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E - Safety of NGTs/NGT-products

* **24. What is your view on the safety of NGTs/NGT-products? Please substantiate your reply**

This has already been discussed, primarily in the answer to Q 21. We emphasise that “views” must be evidence-based.

* **25. Do you have specific safety considerations on NGTs/NGT-products?**

- ( ) Yes
- (●) No

* Please explain why not

As emphasised in our answer to Q 21, safety should be assessed and crops regulated according to product /trait not the specific technology employed.

Please upload any supporting documentation for this section here. For each document, please indicate which question it is complementing

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F - Ethical aspects of NGTs/NGT-products

*** 26. What is your view on ethical aspects related to NGTs/NGT-products? Please substantiate your reply**

We provide the following text, adapted from the 2020 EASAC Commentary 'The regulation of genome-edited plants in the European Union' (https://easac.eu/fileadmin/PDF_s/reports_statements/Genome_Editing /EASAC_Genome-Edited_Plants_Web.pdf):

Ethical problems are raised by conflicting values, by interests that pull in different directions. If and when interests or values clash (when certain values or interests can only be achieved at the expense of others), principles are available that can guide the decision-making. Two such principles with implications for the particular issue of plant breeding are the precautionary principle and the principle of proportionality.

If the precautionary principle implies "do nothing if there are unknown risks", this will halt progress, and doing nothing also entails risks. But if the principle means only "act with caution", it has to be made clear what this means in practice. Safety is obviously important, but so are the benefits. One possibility is to say that it suggests: "act according to the principle of proportionality". The precautionary principle, if strictly interpreted, requires work to stop if there are uncertainties about the risks involved, and it places the burden of proof of safety on those who want to promote a change. But the principle of proportionality is more open, in its four conditions (Hermerén, 2012), which at all times can be discussed, assessed, argued for and applied in the light of the present evidence. Decisions can then be taken, which can be changed as the scientific evidence and value landscape changes:

(1) Importance of objective – the intended goal, theoretical or practical, should be important.

(2) Relevance of means – the means should bring about or at least help to achieve the goal.

(3) Most favourable option – there is no other less controversial or risky means to achieve the goal(s).

(4) Non-excessiveness – the means used should not be excessive in relation to the intended goal – which requires analysis, argument and interpretation.

This suggests an approach, termed stewardship, implying or encouraging an ongoing overview of processes in the light of changing evidence and values within restrictions imposed for example by respect for human rights. From this perspective, there is pressing need to make use of the proportionality principle when introducing reform to strengthen the use of scientific evidence and tackle future uncertainties.

The ethical issues are receiving considerable attention in Member States and the European Commission. The European Group on Ethics in Science and New Technology recently organised a roundtable on gene editing, including plant applications and discussion was clearly polarised. It continues to be important to take the range of public perceptions into account, against a background of contested knowledge, when formulating policy in this area and the forthcoming Opinion to be published by the EGE will be a significant contribution to catalysing further discussion. In the meantime, it is worth noting the general conclusions from the 2009 EGE report 'Ethics of modern developments in agricultural technologies' (https://publications. europa.eu/en/publication-detail/-/publication/9369a035-5a5e-45da-8e37-09717ed806d5/language-en/format-PDF/source-77404379): the goals of food security, safety and sustainability are the guiding principles to

which any agricultural technology must adhere.
The 2020 EASAC Commentary on regulation of genome-edited plants described some recent public survey data indicating the potential for public support for genome editing. These issues were also explored in a 2020 report of the Norwegian Biotechnology Advisory Board, 'Norwegian consumers' attitudes toward gene editing in Norwegian agriculture and aquaculture' (https://www.bioteknologiradet.no/filarkiv/2020/04/Report-consumer-attitudes-to-gene-editing-agri-and-aqua-FINAL.pdf), where a majority of consumer respondents indicated that it can be unethical not to use gene editing in crop plants and livestock if it can contribute towards solving important societal challenges, such as climate adaptation of crops (and the majority of consumers also supported gene editing in organic crop production). The Danish Ethical Council, in their 2019 report 'GMO and ethics in a new era' (https://www.etiskraad.dk/~/media/Etisk-Raad/en/Publications/DCE_Statement_on_GMO_and_ethics_in_a_new_era_2019.pdf?la=da), found similar support of gene-edited crops as part of the response to climate change.

Hermerén (2012) The principle of proportionality revisited: interpretations and applications. Medicine, Health Care and Philosophy 15, 373-382. https://doi.org/10.1007/s11019-011-9360-x

*** 27. Do you have specific ethical considerations on NGTs/NGT-products?**

- ○ Yes
- ◉ No

* Please explain why not

No, nothing further to add on ethical considerations except to emphasise the point that there is a moral obligation to use all available approaches including novel technologies to promote food and nutrition security.

Please upload any supporting documentation for this section here

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G - Consumers' right for information/freedom of choice

*** 28. What is your view on the labelling of NGT-products? Please substantiate your reply**

The 2020 EASAC Commentary and 2019 Statement by the German Academies recognised the importance of enabling freedom of choice for consumers, using consistent labelling rules and transparency in disclosing the process used. We urge a change in focus – from labelling products with information on the method used to grow the product to labelling with information about the environmental and health impacts. Unfortunately, some of the language used in the questions posed in this consultation reinforces what has been the problem for the EU – a misapplied focus on method rather than on product performance and quality. In the case of "NGT-products", the likely divergence between EU labelling of its own products and labelling of products imported by the EU will create new difficulties for the EU that are not in its consumers' interests.

Labelling for health or environmental criteria must be evidence-based but the issues are complex. For example, labelling might help to incentivise the consumption of food products that help to mitigate or adapt to climate change (Godfray et al., 2018). If NGTs help to develop more climate-resilient agriculture, should those benefits be included in their labelling?

Godfray et al. (2018) Meat consumption, health and the environment. Science 361, eaam5324. https://doi.org/10.1126/science.aam5324

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H - Final question

*** 29. Do you have other comments you would like to make?**

- (●) Yes
- ( ) No

Please provide your comments here

The 2020 EASAC Commentary on regulation of regulation of genome-edited plants asks the European Commission to explore the options for radical reform in this area. In particular we emphasise:

- Products of new technology and their use, rather than the technology itself, should be evaluated according to the scientific evidence base.
- If a product of genome editing does not contain foreign DNA, it should not fall within the scope of EU legislation on GMOs.
- There is no time to lose in resolving the problems for food and nutrition security in Europe.
- There is continuing need for wide-ranging engagement to discuss critical issues, including ethical issues, to build trust between scientists and the public.

We conclude by repeating the recommendations from the 2019 Statement of the German Academies 'Towards a scientifically justified, differentiated regulation of genome edited plants in the EU':

- First, to revise the GMO definition/exemptions to enable the EU to capitalise on the plant breeding opportunities afforded by genome editing.
- Secondly, to develop a new legal framework to focus on traits not processes.

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The regulation of genome-edited plants in the European Union

EASAC commentary on the statement by the German National Academy of Sciences Leopoldina, the Union of the German Academies of Sciences and Humanities, and the German Research Foundation

Introduction to new plant breeding techniques

Agriculture continues to face major challenges to deliver food and nutrition security at a time of increasing pressures from social and economic inequity and instability, population growth, climate change and the need to avoid further loss in ecosystem biodiversity. The production of more food, more sustainably, requires the development of crops that can make better use of limited resources and will contribute significantly to attaining multiple Sustainable Development Goals.

In this commentary, the European Academies' Science Advisory Council (EASAC) expresses full support for the recent statement by the German National Academy of Sciences Leopoldina, the Union of the German Academies of Sciences and Humanities together with the German Research Foundation (Leopoldina *et al*. 2019) entitled 'Towards a scientifically justified, differentiated regulation of genome edited plants in the EU', which was prepared in response to the European Court of Justice (ECJ) decision of 2018 (C-528/16). We also note the significance of the recent decision by the European Council (Council of the European Union, 2019) to ask the European Commission to clarify the status of novel genomic techniques with regard to the options to update the existing legislation.

New breeding techniques are emerging rapidly from advances in genomics research, for application in crop improvement. They enable targeted changes in the genome and they have significant potential for the sustainable intensification of agriculture, when used as part of the deployment of all available approaches to achieving food and nutrition security and building on existing good agronomic practice. Unlike chemical- or radiation-induced mutagenesis, often traditionally used for crop improvement tools, the new breeding techniques do not create multiple, unknown, unintended mutations throughout the genome. Furthermore, the products of the new breeding techniques are also unlike genetically modified organisms (GMOs) used in agriculture, in being more precisely targeted and having no foreign DNA in the end product. Advances in plant genome editing may also support other applications for the Bioeconomy in support of European competitiveness (see later).

The scientific opportunities coming into range in plant breeding, for example, to develop more climate-resilient agriculture, resistant to the increasing abiotic

and biotic stresses, have been examined previously by EASAC (for example EASAC 2017a, 2017b) and have been explored extensively in the scientific literature (for example, the recent comprehensive review by Bailey-Serres *et al*. (2019)).

ECJ decision and the German statement recommendations

In 2018, the ECJ decided that organisms obtained by the new techniques of genome editing are GMOs within the meaning of the Directive 2001/18/EC on the release of GMOs into the environment, and they are subject to the obligations in the legal framework laid down by the GMO Directive. This ECJ declaration has been controversial (see, for example, Holme *et al*. 2019) and the background to this judgement with implications for EU science, innovation and regulation have been discussed in detail in the scientific and policy communities, for example the Group of Chief Scientific Advisers to the European Commission (2018). Their GCSA Opinion observed that new scientific knowledge has made the GMO Directive no longer fit for purpose, that the current approach does not properly respect the motivation behind the precautionary principle for ensuring product safety, and that the regulatory framework should put the emphasis on the features of the end product rather than on the production technique.

The recent German institutions' statement provides detailed assessment of the history of molecular breeding methods in agriculture, of the current research and innovation regulatory approaches used worldwide, with particular regard, for example, to issues for safety assessment and for intellectual property protection. The German statement also examines the consequences, particularly for world trade, arising from lack of consistency in regulatory approaches and the problems for product verifiability. In response to the ECJ decision, Leopoldina *et al*. (2019) propose a range of coordinated recommendations to reform EU genetic engineering law that would take account of science-based criteria in the approval process. These reforms require concomitant action to strengthen science and competitiveness in the EU (Box 1).

These recent recommendations that include concrete textual suggestions for the amendment of EU genetic engineering law are consistent with messages emerging

Box 1 Summary of recommendations from Leopoldina *et al*. (2019)

The first step is to amend EU genetic engineering legislation to include revising the GMO definition, or the associated exemptions, in order to exempt genome-edited organisms from the scope of the legislation if (1) no foreign genetic information is inserted and/or (2) if there is a combination of genetic material that could also result naturally or through traditional breeding methods.

Beyond the short-term amendment of current genetic engineering legislation, a second step should comprise developing a fundamentally new legal framework that is detached from the previous process-based regulatory approach. The new, science-based, legal framework must link the requirements of authorisation and registration to the resulting traits.

To ensure continuing development of the science base and responsible innovation in agriculture, it is also important for the European Commission and Member States to do the following.

Make field trials of new crop varieties practicable again as quickly as possible.

Support public engagement about new breeding methods, to take account of, and inform, consumer views.

Enable freedom of choice by consumers, using consistent labelling rules.

Provide broader support for responsible innovation in agriculture, e.g. by public funding of research on the health, environmental, economic, ethical and societal consequences of products and application scenarios of new molecular breeding methods. Support for innovation must also ensure that the precautionary principle is not linked to speculative risks but rather applied in the context of potential benefit-risk considerations and the risk of doing nothing.

Increase market competition by targeted incentives with particular regard to small and medium-sized enterprises currently deterred by high bureaucratic and cost obstacles.

Source: Leopoldina *et al*. (2019) with summarising by EASAC of original text on recommendations.

from EASAC work during the past two decades (EASAC 2004, 2011, 2013, 2015, 2017a, 2017b, 2018) and, indeed, with other international policy development initiatives. In addition to the international examples that the German statement cites for different regulatory approaches outside the EU (and the likelihood of increasing divergence) can be added the example of Australia and New Zealand. There, very recent recommendations from the Food Standards Authority (2019) include a proposal to revise and modernise definitions in the Code for food produced using gene technology, to ensure that new breeding techniques are regulated in a manner commensurate with the risk that they pose.

The development of strategic options for the EU has to reflect the increased knowledge derived from an ever-faster pace of science together with the accumulating experience worldwide on the use of modern molecular methods to understand plant biology. Significant opportunities are described in the German statement, including genome-edited crops already marketable elsewhere with benefits for nutrition and productive, low-pesticide and resource-conserving agriculture. In addition, there is collective need to do more to understand the genetic diversity existing naturally within a species. Although the core genome is shared by all varieties within a species, individual varieties will differ in other genes such that there may well be more, and more significant, differences between two conventional varieties than between a conventional variety and its edited counterpart.

In this brief commentary, EASAC endorses the recommendations summarised in Box 1 and takes this opportunity to update and reiterate some of our previous messages.

Global implications

It is crucially important to take account of the changing world as well as scientific advances when reflecting on policy options. EU reforms in the regulation of plant breeding are urgently needed if the objectives for EU innovation are to be met, including those for the Common Agricultural Policy, the Green Deal, and the Bioeconomy. It must also be appreciated that EU policy decisions have very significant implications elsewhere in the world. In the past, for example, the EU over-regulation of GMOs had negative impact on science and innovation in developing countries who feared for their export markets and who had been inclined to look to the EU to express leadership in research and development. This EU deterrent to innovation in developing countries can be perceived as undermining EU development policies aiming to build international collaboration in science and technology. These problems for food and nutrition security and sustainability in the rest of the world created by EU decisions are compounded by the EU exporting its lack of agricultural sustainability (EASAC, 2013, 2017b), partly in consequence of not employing on its territory all available technologies for sustainable intensification.

Given the escalating, shared, problems associated for example, with climate change, it is vital that EU actions take account of our responsibilities in the global context and that we do not repeat our past mistakes in failing to capitalise on advances in the biosciences.

Addressing policy disconnects

In addition to the disconnect noted above between EU development policy objectives for science and technology collaboration, and the consequences of over-regulated and inconsistent GMO policy, EASAC has previously emphasised (EASAC 2013, 2018) other contradictions which undermine the EU desire for coherent strategy to address major societal challenges. These contradictions include those between:

- The European Commission's leadership in support for science *and* those regulatory impediments to innovation that are felt most strongly in academia and the small and medium-sized enterprises. EU citizens are poorly served if their contribution to the funding for cutting edge science does not lead to them benefitting from the knowledge generated.

- The productivity goals for EU climate-resilient agriculture (for planetary health) that also protects human health *and* the practical difficulties in using all appropriate technologies to respond to climate change.

- The environmental goals for EU agriculture to reduce the external application of chemicals (fertilisers, pesticides and herbicides) *and* the impediments to identifying and breeding new crop varieties that require less application of such chemicals. The United Nations Year of International Plant Health in 2020 is particularly relevant for reaffirming the contribution that improved plant breeding can make to plant and planetary health. The EU could provide leadership globally to reduce the use of pesticides and fertilisers as well as mitigating the impact of environmental change on food sustainability.

- The current EU practice of importing genetically modified food and feed that is not approved for cultivation on EU land: the consequences of this also run counter to EU aspirations to limit 'food miles'. Unless the EU response to climate change includes developing climate-resilient agriculture, it can be foreseen that the EU will require to import more food and feed, and an increasing proportion

of this is likely to be from the use of new breeding techniques elsewhere in the world.

Ethical issues and proportionality

EASAC has previously highlighted (EASAC, 2017a) how there is a moral obligation to fight disease and relieve suffering. To the extent that genome editing technologies provide useful tools to achieve such purposes, there is an opportunity cost in using them too late or not at all, particularly if they are safer, more effective and cheaper than alternative technologies.

Ethical problems are raised by conflicting values, by interests that pull in different directions. If and when interests or values clash (when certain values or interests can only be achieved at the expense of others), principles are available that can guide the decision-making. Two such principles with implications for the particular issue of plant breeding are the precautionary principle and the principle of proportionality.

If the precautionary principle implies 'do nothing if there are unknown risks', this will halt progress, and doing nothing also entails risks (EASAC, 2015). But if the principle means only 'act with caution', it has to be made clear what this means in practice. Safety is obviously important, but so are the benefits. One possibility is to say that it suggests: 'act according to the principle of proportionality'. The precautionary principle, if strictly interpreted, requires work to stop if there are uncertainties about the risks involved, and it places the burden of proof of safety on those who want to promote a change. But the principle of proportionality is more open, in its four conditions (Hermeren, 2012), which at all times can be discussed, assessed, argued for and applied in the light of the present evidence. Decisions can then be taken, which can be changed as the scientific evidence and value landscape changes:

1. *Importance of objective* — the intended goal, theoretical or practical, should be important.

2. *Relevance of means* — the means should bring about or at least help to achieve the goal.

3. *Most favourable option* — there is no other less controversial or risky means to achieve the goal(s).

4. *Non-excessiveness* — the means used should not be excessive in relation to the intended goal, which requires analysis, argument and interpretation.

This suggests an approach, termed stewardship, implying or encouraging an ongoing overview of processes in the light of changing evidence and values within restrictions imposed for example by respect for human rights. However, experience of GMO Panel members of the European Food Safety Authority (Casacuberta and Puigdomenech, 2018) indicates that there has been a reduction in the flexibility of the risk assessment procedures for GMO crop applications, even while the evidence base worldwide (including the substantial evidence for lack of harm) has accumulated. From this perspective, there is pressing need to make use of the proportionality principle when introducing reform to strengthen the use of scientific evidence and tackle future uncertainties.

The issues are receiving considerable attention in Member States and the European Commission. For example, the Opinion published in France by the Ethics Committee of INRA (2016) provided an important perspective on the link between agricultural and environmental considerations. The European Group on Ethics in Science and New Technology recently organised a roundtable on gene editing, including plant applications (EGE, 2019) and discussion was clearly polarised. It continues to be important to take the range of public perceptions into account, against a background of contested knowledge, when formulating policy in this area (see next section) and the forthcoming Opinion to be published by the EGE will be a significant contribution to catalysing further discussion.

Public opinion

Public discussion about GMO crops tended to become a proxy for other much-needed discussion about food security and safety, farming systems, fair competition, social justice, the economic power of multi-national companies and the apparent conflict between intellectual property protection and benefit sharing (EASAC, 2013). If the differing public values are to be better understood as part of attempts to reconcile them and if we wish to avoid repeating the same mistakes in public engagement on genome editing, then the multiple determinants of each controversy need to be made more transparent. It is also vitally important to learn lessons from history: an inadvertent consequence of EU GMO legislation and the high costs inherent in seeking regulatory approval has increased multi-national company monopoly in the commercial agricultural model. The Leopoldina *et al*. (2019) statement highlights the importance of increasing market competition by targeting incentives for smaller companies. Competition might also be enhanced by further exploration of the options for protecting intellectual property rights to take account of the issues for maintaining co-existence between breeder's rights and patents (EASAC, 2013). Plant Breeders Rights provides a well tried and tested system whereby breeders can secure financial returns on the release of a successful variety without jeopardising future societal benefits to be derived by even further genetic improvement that might be achieved by others.

It is beyond the scope of this short commentary to discuss in detail the varying public perceptions on genome editing in plants but it is worth mentioning that public surveys in the UK, commissioned on behalf of the Royal Society (van Mil *et al*. 2017)[1] demonstrate significant public support. For example, there was support for the use of genome editing to prevent crop damage by fungal diseases (77% of the group surveyed), to make crops more nutritious as a way of supplementing poor diets (70%) and in the biosynthesis of cheaper medicines (69%). Of course, these high approval ratings are expressed subject to necessary conditions: the use of genome editing as part of a package of solutions, with equitable access, no harm to the environment, publicly accessible information, effective regulation and ethical guidance in place.

It may be inferred that public opinion in many EU Member States is willing to consider the benefits of crop genome editing judging from the initiative of 14 countries, led by the Netherlands and Estonia. The advice from the Dutch agricultural ministry and others, following the ECJ ruling calls for the reform of GMO laws with regard to new breeding techniques, also observing that organisms obtained by mutagenesis have been used in farming for many years and have a long safety record[2]. As emphasised recently by former EU Health Commissioner Vytenis Andriukaitis[3], there is need for continuing dialogue with all sectors in society in the necessary rethinking of the cumbersome policy that currently deters new breeding techniques, '*yet this talk should not be at the expense of science and innovation*'. In the view of EASAC, dialogue does not need to continue to be primarily about the value of genome editing technologies, or GMOs, because this value is already demonstrable. Rather we need to debate about how the value of these technologies can be obtained for the EU and how the EU can contribute to achieving global food and nutrition security.

Other applications of new plant breeding techniques

Agricultural biotechnology, including genome editing, has potential to contribute to societal objectives in pursuit of the Bioeconomy in other ways in addition to food and nutrition security, for example in the search for the next generation bioenergy and in the biosynthesis of medicinal products, other high value chemicals and the building blocks for renewable industrial synthesis (see, for example, Tatsis and O'Connor, 2016; Liu *et al*. 2017; Mortimer, 2019; Najera *et al*. 2019).

Summary of EASAC messages

EASAC endorses the Leopoldina *et al*. (2019) recommendations and now also reiterates our core recommendations on new breeding techniques from the previous EASAC work (2015, 2018):

- Products of new technologies and their use, rather than the technology itself, should be evaluated according to the scientific evidence base.
- The potential costs of not using a new technology, or being slow in adoption, must be acknowledged. There is no time to lose in resolving the problems for food and nutrition security in Europe.
- If a product of genome editing does not contain foreign DNA, it should not fall within the scope of EU legislation on GMOs.
- More broadly, there should be full transparency in disclosing the process used and the EU should seek to regulate the trait and/or product rather than the technology used in generating that product. That is, when considering safety issues, the focus should be on assessing whether the novel attributes of the plant might represent a risk to the environment or human health, irrespective of the breeding technique employed.
- The European Commission should continue to commit to supporting fundamental research in plant sciences to provide the tools and other resources for future innovation in plant breeding and farming practices.
- There is also continuing need for wide-ranging engagement to discuss critical, including ethical, issues to build trust between scientists and the public.

EASAC directs our messages to the European Commission, Council and Parliament and to policy makers in the Member States. The request by the European Council to the European Commission to clarify options to update the existing legislation might be interpreted minimally by some only as an examination of how to deal with products where the mode of molecular change cannot be detected, but in our view, this would then be a missed opportunity. The request from the Member States should rather be viewed as an invitation to the European Commission to set out

[1] This research involved use of focus groups with a broad demographic of participants plus a quantitative online survey (n = 2,000) to validate the dialogue findings.
[2] 14 EU countries call for 'unified approach' to gene editing in plants, www.euractiv.com, 24 May 2019.
[3] Andriukaitis: Europe should take lead in science-based plant innovation, www.eurativ.com, 4 December 2019.

the strategic options for EU agricultural innovation and responsibilities in the wider international context, leading to a reopening of Directive 2001/18/EC. EASAC reaffirms the importance of exploring radical reform and urges the EU Institutions to explore the options recommended by Leopoldina *et al*. (2019) and others:

- First, to revise the GMO definition/exemptions to enable the EU to capitalise on the plant breeding opportunities afforded by genome editing.
- Secondly, to develop a new legal framework to focus on traits not processes.

Reform is needed urgently: if provision is not made soon for an evidence-based flexible and proportionate regulatory framework, there is little prospect of agricultural innovation realising its potential in achieving the Sustainable Development Goal targets by 2030 or of the EU maintaining international competitiveness.

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EASAC

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Its mission reflects the view of academies that science is central to many aspects of modern life and that an appreciation of the scientific dimension is a pre-requisite to wise policy-making. This view already underpins the work of many academies at national level. With the growing importance of the European Union as an arena for policy, academies recognise that the scope of their advisory functions needs to extend beyond the national to cover also the European level. Here it is often the case that a trans-European grouping can be more effective than a body from a single country. The academies of Europe have therefore formed EASAC so that they can speak with a common voice with the goal of building science into policy at EU level.

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EASAC covers all scientific and technical disciplines, and its experts are drawn from all the countries of the European Union. It is funded by the member academies and by contracts with interested bodies. The expert members of EASAC's working groups give their time free of charge. EASAC has no commercial or business sponsors.

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To find out more about EASAC, visit the website – www.easac.eu – or contact the EASAC Secretariat at secretariat@easac.eu

EASAC, the European Academies' Science Advisory Council, consists of representatives of the following European national academies and academic bodies who have issued this commentary:

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Science Advisory Council

Planting the future: opportunities and challenges for using crop genetic improvement technologies for sustainable agriculture

EASAC policy report 21

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building science into EU policy

EASAC

EASAC – the European Academies Science Advisory Council – is formed by the national science academies of the EU Member States to enable them to collaborate with each other in giving advice to European policy-makers. It thus provides a means for the collective voice of European science to be heard.

Its mission reflects the view of academies that science is central to many aspects of modern life and that an appreciation of the scientific dimension is a pre-requisite to wise policy-making. This view already underpins the work of many academies at national level. With the growing importance of the European Union as an arena for policy, academies recognise that the scope of their advisory functions needs to extend beyond the national to cover also the European level. Here it is often the case that a trans-European grouping can be more effective than a body from a single country. The academies of Europe have therefore formed EASAC so that they can speak with a common voice with the goal of building science into policy at EU level.

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Cover image: Germination, the initial stage in the continuous processes of plant development

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Foreword

The world continues to face major problems in aiming to deliver food security alongside increasing pressures from population growth, climate change and economic and social instability. Global problems require global action and, collectively, we should use the best science, technology and innovation to tackle the challenges. The European Union (EU) is not immune from the problems and must do more to establish innovation in agriculture, to satisfy a greater proportion of domestic demands for food, feed and the other products of the bioeconomy while, at the same time, contributing research and innovation to help resolve the global challenges.

Many of the academies of science in Europe have previously drawn attention to the role that biosciences can play in the sustainable intensification of agriculture: improving efficiency in production and avoiding further loss of biodiversity. Previous work by the European Academies Science Advisory Council (EASAC) has highlighted the importance of better characterising, conserving and using plant genetic resources for food and agriculture. The present report makes the case for using crop genetic improvement technologies for enhanced agricultural production. This need is immediate. EASAC also emphasises that these paths to innovation should be combined with the deployment of all available approaches, traditional and novel, building on existing achievements for good agronomic practice.

Our report draws on the ever-accumulating scientific evidence that continues to define both the current attainments of crop genetic improvement technologies, including genetic modification (GM), and the potential value that can accrue by capitalising on the scientific opportunities now coming within range. The large body of international experience gained from different strategies and practices helps to reduce uncertainties about the impact of new technologies in agriculture.

In conducting our analysis of the international evidence and determining the implications for the EU, we initiated two work streams to bring together the available data. First, we analysed findings from certain other countries that are actively adopting biotechnology, to ascertain the socio-economic and scientific impacts of taking different policy decisions. Secondly, in conjunction with our colleagues in the Network of African Academies (NASAC), we examined the current situation for agricultural biotechnology in Africa and the consequences for developing countries of policy choices made in the EU. Our report recommends that current policy disconnects within the EU, acting to impede food security and trade, must be tackled. In particular, the framework for regulation of agricultural innovation must be revisited and reformed to take account of the new evidence and expertise emerging worldwide.

It is noteworthy that a recent joint statement* from governments in the Americas and Australia on innovative agricultural production technologies, focusing on plant biotechnology, states the intention to work collaboratively to '*promote the application of science-based, transparent and predictable regulatory approaches that foster innovation and ensure a safe and reliable global food supply, including the cultivation and use of agricultural products derived from innovative technologies*'. We commend this initiative to EU policy-makers as something they should consider strongly supporting.

We address recommendations from our report to policy-makers at the EU level, in the European Commission, European Parliament and Council of Ministers, and in the Member States, where these matters also require urgent attention. As these issues are of great relevance worldwide, we will continue to stimulate analysis and debate through other academy networks.

A founding principle of EASAC is that objective scientific advice must be independent of vested – political, industrial or other – interests. In all of our work we strive in a transparent manner to inform the policy-maker and other stakeholders of the options available and their foreseeable consequences. Because some of the matters covered in our report have long been controversial, our project has involved a wide range of scientists from across the EU and beyond. The report has been prepared by consultation with a Working Group of academy-nominated experts acting in an independent capacity. I thank the members of this Working Group for their continuing commitment in exploring difficult issues and their considerable support in helping EASAC compile this report. I also thank our colleagues in NASAC and the expert speakers at our joint workshop for their significant contributions to the project. I thank our independent referees for their assistance in ensuring the quality of the report and the academies in our chosen comparator countries for their review of our analysis and conclusions. In addition, I thank our EASAC colleagues on Council and the Biosciences Steering Panel for their guidance in designing the project and delivering key messages. I thank the InterAcademy Panel for their support in funding the project and the John Templeton Foundation and the

* Joint Statement on Innovative Agricultural Production Technologies, particularly Plant Biotechnologies by Governments of Argentina, Australia, Brazil, Canada, Paraguay and the USA, April 2013, available at http://www.fas.usda.gov/itp/biotech/LM%20statement%20on%20innovative%20ag%20-%20GE%20crops%20-%20Final%20April%202013%20endorsements.pdf.

Malaysian Cambridge Studies Centre for their specific financial contributions to the workshop in Addis Ababa.

We welcome discussion of any of the points that we have raised in this report, with the objective of increasing the impetus for evidence-based policy development. In closing, I emphasise that more public engagement is vitally important if we are to be successful in using agricultural innovation to deliver food security and capitalise on the other outputs of the bioeconomy. In previous work in this area, many of our academies and our scientific contributors have been actively engaged in discussing key issues with the community-at-large. It is important to build on this public dialogue to ensure that policies are based on a shared version of the future and to explore appropriate governance frameworks to include stakeholders and members of the public. EASAC will continue to encourage such engagement with the public, to stimulate debate and inform expectations, about the matters raised here to facilitate the exchange and wise application of knowledge.

Professor Sir Brian Heap
EASAC President

Summary

Agriculture faces major challenges to deliver food security at a time of increasing pressures from climate change, social and economic inequity and instability, and the continuing need to avoid further loss in ecosystem biodiversity. The introduction of new EU legislation requiring farmers to reduce reliance on crop protection chemicals creates additional challenges for maintaining levels of crop productivity.

Previous European Union (EU) agricultural policy had focused on constraining food production but there is a new realisation that the EU should now increase its biomass production for food, livestock feed and other uses, including renewable materials to support the bioeconomy. The production of more food, more sustainably, requires the development of crops that can make better use of limited resources. Agricultural innovation can capitalise on the rapid pace of advance in functional genomics research and it is unwise to exclude any technology *a priori* for ideological reasons. Sustainable agricultural production and food security must harness the potential of biotechnology in all its facets.

In previous work, the European Academies Science Advisory Council (EASAC) has described the opportunities and challenges in using plant genetic resources in improved breeding approaches, for example by using marker-assisted selection of desired traits. In the present report, EASAC explores some of the issues associated with the genetic modification of crops, where the EU has fallen behind in its adoption of the technology, compared with many other regions of the world. Concerns have been expressed that a time-consuming and expensive regulatory framework in the EU, compounded by politicisation of decision-making by Member States and coupled with other policy inconsistencies, has tended to act as an impediment to agricultural innovation. Controversies about the impact of genetically modified (GM) crops have too often been based on contested science or have confounded effects of the technology with the impact of agriculture *per se* or changes in agronomic practice. It is vital to address the policy disconnects because there is a wide range of opportunities in prospect for improving agricultural productivity and efficiency, environmental quality and human health, by using all available technologies where appropriate.

Previous work by member academies of EASAC has documented where there is excellent, relevant science to be nurtured and used, and where problems have arisen because of the failure to use science to inform the modernisation of regulatory approaches to benefit–risk assessment. The goal of the present report is to clarify the implications for policy-makers of alternative strategic choices in using the tools, collectively termed crop genetic improvement technologies, for delivering sustainable agriculture. Our analysis of the international evidence draws on two main work streams:

- A case study comparison of certain countries (in the Americas and Asia) who have taken a different path by their decision to adopt GM crops more actively. We review the documented impacts in terms of environmental and socio-economic indicators, and the implications for the science base, and note that comparing different regulatory approaches used elsewhere might offer new insight for EU policy-makers.

- A collaboration with the Network of African Science Academies (NASAC) to ascertain the current situation regarding crop genetic improvement strategies in African countries and the implications of EU practices and perspectives on decisions in Africa. The situation across Africa is diverse but there are now major initiatives to use GM crops to address local needs. There is evidence that European influences have sometimes constrained the use of such technologies in Africa but there are significant opportunities for international partnership, informed by local priorities and acting to strengthen local systems.

The EASAC Working Group also provided detailed evaluation of a broad range of current issues within the EU, relating to regulatory reform, consequences for the science base and new technology development (particularly, the New Breeding Techniques), public engagement, intellectual property and open innovation, increasing environmental challenges, the potential food crop pipeline and new applications for the bioeconomy. This broad review of issues revealed several serious inconsistencies in current EU policy. For example, an important objective to reduce pesticide use in agriculture is being implemented without sufficient attention paid to facilitating the development of alternative methods for protecting crops from pests and diseases. Bringing together analysis of the cross-cutting issues for the EU and the international evidence, the EASAC Working Group reached four main conclusions, with extensive implications for ascertaining greater coherence in policy-making. These are described below.

1. Land use and innovation: the EU needs to increase its production and productivity of plant-derived biomass for food, feed and other applications, thereby decreasing dependency on imports and reducing the regional and global environmental impact. Commitment to agricultural innovation can be expected also to create jobs, benefit

rural development and contribute to a growing gross domestic product. Biotechnology for crop improvement must be part of the response to societal challenges. The EU is falling behind new international competitors in agricultural innovation and this has implications for EU goals for science and innovation and the environment as well as for agriculture. There is need to improve public awareness of the scientific, environmental, economic and strategic issues to help support better informed individual choices, national political debate and EU priority-setting. The goal is to move from the current situation where the passive customer merely tolerates technologies to one where the active citizen appreciates technologies.

2. Regulation: in common with other sectors, the aim should be to regulate the trait and/or the product but not the technology in agriculture. The regulatory framework should be evidence-based. There is no validated evidence that GM crops have greater adverse impact on health and the environment than any other technology used in plant breeding. There is compelling evidence that GM crops can contribute to sustainable development goals with benefits to farmers, consumers, the environment and the economy. Action is needed to unify and harmonise the regulatory and innovation-enabling roles of the EU policy-making institutions and to ensure that regulation of the outputs of all the crop genetic improvement technologies has a firm foundation in sound science.

3. Promoting competition: the current slow and expensive regulatory situation surrounding GM crops in the EU encourages monopolies. It is important to explore ways to stimulate open innovation and reformulate the regulatory framework so as to encourage smaller companies and public sector activities.

4. The global context: EU policy actions influence the developing world and the wider consequences need to be taken into account when deciding EU strategic options. There is evidence that attitudes to GM crops in the EU have created difficulties for scientists, farmers and politicians in Africa and elsewhere. Establishing the necessary policy coherence between EU domestic objectives and a development agenda based on partnership and innovation is important for the developing world as well as for Member States.

EASAC judges that the potential benefits of crop genetic improvement technologies are very significant. Capturing these benefits should be a matter for urgent attention by EU policy-makers, alongside the development of indicators to monitor success in attaining the objectives (for example for efficient and diversified land use). Based on the preceding conclusions, EASAC recommendations cover the following areas.

Regulatory framework: the European Commission, together with the other EU Institutions should re-examine its current policy and principles governing the broad area of agricultural innovation. This should include for example, the integration of GM crop objectives with integrated pest management strategies, and should address the multiple policy disconnects that are leading to inconsistency in precepts and inefficiency in performance. The regulatory framework must be reformulated appropriately to be science-based, transparent, proportionate and predictable, taking into account the extensive experience gained and good practice implemented worldwide. There is need for urgent action to agree the status and regulation of New Breeding Techniques and, in particular, to confirm which products do not fall within the scope of legislation on genetically modified organisms.

Public engagement: the scientific community must clearly articulate the consequences of research findings and the opportunities for agricultural innovation. As part of this engagement, EASAC and its member academies will continue to stimulate discussion with citizens about the key issues raised in this report.

Research and development: opportunities created by Horizon 2020, the European Research Council and European Research Area are extremely valuable for pursuing priorities in plant sciences and related disciplines, and can help to attract smaller companies as well as the public sector to contribute to the knowledge-based economy. There are additional, infrastructural issues to tackle in support of innovation: (1) although the relevant science base is still strong in some Member States, there is need to support skills provision and researcher career development, including reversing the decline in some key scientific disciplines and reducing the permanent loss of scientists to countries outside the EU; (2) revitalising public sector plant breeding efforts and creating opportunities for collaboration between the public and private research sectors with the translation of scientific outputs to improved agricultural practices; (3) clarifying the options for intellectual property protection and open innovation; (4) further increasing partnership between scientists in the EU and developing countries.

International partnership: the EU can learn from the rest of the world in characterising and implementing good regulatory practice, while it must also acknowledge the international impact of its policies and perspectives. There are new opportunities for sharing experience and engaging in international research. EASAC stands ready to continue playing its part in identifying these opportunities and stimulating further debate.

1 Introduction

1.1 Global societal challenges

A billion people experience hunger and another billion lack essential vitamins and minerals in their diet (FAO, 2010; Fan and Olofinbuyi, 2012). Agriculture faces some major inter-connected challenges in delivering food security; sustainably balancing future supply and demand, at a time of increasing pressures from population growth, changing consumption patterns and dietary preferences, and post-harvest losses. These problems are compounded by climate change, social and economic inequity and instability, and the continuing imperative to avoid further loss in ecosystems biodiversity (IAASTD, 2008; Godfray et al., 2010). One-quarter of all agricultural land is highly degraded, yet over the next 40 years, agricultural production must increase by 60%, sustainably and with fairer distribution, to provide global food security, a major contributor to social stability (OECD–FAO, 2012). At the same time, there are growing opportunities and demands for the use of biomass to provide additional renewables, for example energy for heat, power and fuel, pharmaceuticals and green chemical feedstocks.

The European Union (EU) is not immune from these challenges for food and other products (European Commission, 2011b) and there are particular problems regarding the sustainability of current agricultural practices in terms of water and fertiliser use, the degradation of land with deterioration in soil quality and loss of other natural resources. The introduction of new EU legislation requiring farmers to reduce reliance on crop protection chemicals creates additional challenges for maintaining levels of production. For at least the past decade, yield increases on farms have been limited or static for most major crops in the EU (House of Lords European Union Committee, 2010) despite the increasing genetic potential provided by improved varieties and evident from trial plots. The need to increase agricultural productivity and efficiency in developed as well as in developing countries is now well accepted and this will require policy and action to capitalise on the scientific advances that have emanated from recent publicly funded investment in the EU and elsewhere.

Previous EU Common Agricultural Policy (CAP) measures focused on constraining production. The lack of political priority to generate greater efficiency in the EU has inevitably led to considerable exploitation of land mass outside EU borders for EU needs; this is estimated to be equivalent to the size of Germany (about 35 million hectares; von Witzke and Noleppa, 2010). As well as being a significant exporter, the EU is now the world's largest importer of agricultural commodities. Currently less than half of the food and feed consumed in the EU is produced within its borders (EASAC, 2012). However, EU policy is changing to support food security (European Commission 2011b; Joint Research Centre, 2011). Better use of advances in science can help to close the present gap between supply and demand, enabling the EU both to generate a higher proportion of its domestic food requirements and to contribute solutions to the global food and feed challenges.

1.2 The strategic framework for generating and using science

The sustainable production of more food requires crops that can make better use of limited resources, including land, water and fertilisers. The necessary strengthening of innovation in agricultural production systems will require a new commitment to research, education, infrastructure and extension services (OECD–FAO, 2012). Capitalising on the improved use of plant genetic resources is seen as a critical part of the necessary response to the challenges for food and farming. No new technology should be excluded *a priori* on ideological grounds (Pretty, 2008; Government Office for Science, 2011).

Historically, EU researchers have played a major role in advancing the multi-disciplinary science that is essential for agricultural innovation, but they need to be encouraged to continue doing so. The European Commission has already recognised that efforts to increase agricultural research can be an important part of ensuring food security (European Commission, 2008). However, the increased requirement for innovation has yet to be aligned with the reform of CAP or with biodiversity and rural development activities that can also do more to support genetic diversity in agriculture (European Commission, 2011a). Even though its main focus is on industrial biotechnology, the European Commission's adoption of the Bioeconomy Strategy for Europe (European Commission, 2012a) is welcome in encouraging further investment in research and innovation as well as advocating reinforcement of a coherent policy framework and market conditions in delivering food security. However, as the European Commission Staff Working document accompanying the Strategy (European Commission, 2012b) observes, there are justified concerns about the long-term competitiveness of European industry for the bioeconomy, increasingly losing out to other players, '*… thus it has already lost leadership in plant biotechnology*'. This assessment is realistic, if disappointing: at the onset of the biotechnology era more than three decades ago, Europe was competitive with the USA in plant genetic research. It is vital that sustainable agricultural production and food security harnesses the potential of biotechnology in all its facets. There are still considerable strengths in the underpinning sciences in many Member

States, although erosion in others, and the EU can revive its efforts to become globally competitive again in plant science and its application in biotechnology. The rapid pace of advance in sequencing, genomics and other 'omics' technologies is generating information that is providing new opportunities and technologies to develop improved crops displaying novel combinations of traits. Moreover, high-quality science is important, not only to drive innovation, but also to inform rational policy decisions.

1.3 Adopting new technologies

EASAC has a longstanding interest in issues relating to agriculture and the environment. In previous work we described the opportunities and challenges presented by genomic research to facilitate more efficient crop breeding as an important component of future food production (EASAC, 2004). We also provided a detailed analysis of the steps necessary to identify, conserve, characterise and use plant genetic resources in improved breeding strategies as well as to understand fundamental aspects of plant biology, including genome organisation and plant speciation (EASAC, 2011). Conventional crop breeding has relied historically on lengthy and relatively imprecise techniques but application of modern biosciences, including biotechnology, have the potential to transform agriculture. The modern scientific basis of all crop improvement is the identification of genes that determine a specific trait or crop phenotype. Genetic improvements to crops can be achieved by advanced conventional breeding, for example using marker-assisted selection of desired traits, discussed in detail in our previous work (EASAC, 2004, 2011), by chemical- or radiation-induced mutation breeding (Podevin et al., 2012) and, more recently, by genetic modification. It is to this latter approach that we now turn our attention in the present report (see Appendix 1 for details of the expert Working Group). Approaches based on applications of biotechnology have already improved agricultural productivity worldwide and have very much more to contribute to resilient global food production (Godfray et al., 2010).

Following more than 25 years of experience worldwide, there is an accumulating evidence base on the impact for the first generation of genetically modified (GM) crops, endowed with traits for herbicide tolerance or insect resistance, or both. For the future, a wide range of opportunities for generating better crops, for improving agricultural productivity and efficiency, environmental quality and human health, are in prospect and these opportunities will be discussed subsequently in this report.

The current situation is summarised in Box 1 (and discussed in further detail in Chapter 2). It is noteworthy that few of the GM crops developed hitherto have provided significant potential economic benefit to EU agriculture. This may be one contributory factor to why it has been possible for the EU substantially to reject the adoption of GM crops, an issue that is discussed at length in Chapter 4. The lack of enthusiasm within the EU for the adoption of a GM approach to crop improvement has serious consequences for increasing dependency on food and feed imports, and for the science base, industry competitiveness and the bioeconomy more broadly, as will be discussed subsequently. It should also be appreciated that the potential importance and value of GM technology is influenced by the impact of other policy decisions in agriculture. For example, the recently introduced regulations on the registration

Box 1 The current status of GM crops worldwide

(1) In 2012, 17.3 million farmers planted GM crops. The area so cultivated has increased 100-fold since 1996: from 1.7 million to 170 million hectares in 2012.

(2) Global GM adoption rates are now greater than 80% for both soybean and cotton.

(3) Twenty-eight countries planted GM crops in 2012: 20 were developing countries. The top ten countries each grew more than one million hectares. In 2012, for the first time, the area of GM crops in the developing countries (52% of worldwide total) exceeded that in developed countries.

(4) It was estimated that in 2011, economic benefits to developing countries were US$10.1 billion compared with US$9.6 billion for developed countries. In addition, the socio-economic and environmental impacts of GM crops in contributing to food and feed security, farmers' income, conservation of biodiversity, reduction of agriculture's environmental footprint and mitigation of climate change are increasingly well established (ISAAA, 2013).

(5) Only two GM crops are approved for commercial cultivation in the EU: *Bacillus thuringiensis* (Bt)-insect-resistant maize and modified starch composition potato for industrial use. The total area of GM maize grown in the EU in 2012 was129,000 hectares; Spain contributed more than 90% to this total.

(6) The EU imports about 20 million metric tonnes each year of feed derived from GM crops, mostly soybean, equivalent to about 7 million hectares of agricultural area. This represents more than 70% of EU animal protein feed requirements.

Sources: Brookes and Barfoot, 2012; James, 2012; Marshall, 2012; ISAAA, 2013.

of pesticides will result in a smaller number of active chemical ingredients. This will lead to greater difficulty in the delivery of effective, robust, pest and disease control for farmers who are reliant on chemical-based programmes to return economic yields. The EU has been at the forefront of the basic research on plant defence mechanisms that could support development of alternative genetic-based approaches to crop protection.

1.4 Assessing impact of new technologies

Much effort has been devoted to analysing the productivity and environmental and socio-economic impacts of the first generation of GM crops. This analysis has included assessment of yield, ease and predictability of crop management, applied herbicide use and resultant soil conditions, use of pesticides, crop mycotoxin contamination, farmer income and farmer health (Qaim, 2009; National Research Council, 2010; Brookes and Barfoot, 2012; James, 2012; Mannion and Morse, 2012; ISAAA, 2013). The peer-reviewed results from some of the socio-economic and environmental assessments will be discussed in more detail in subsequent chapters of the present report. In aggregate, the conclusion from the scientific literature is that there is no validated evidence to associate the first generation of GM crops, that have been cultivated for more than 15 years worldwide (and commercialisation was dependent on more than 20 years of prior art in plant sciences), with higher risks to the environment or for food and feed safety compared with conventional varieties of the same crop (DG Research, 2010a; Fagerstrom et al., 2012).

Statements about the adverse impacts of GM crops have too often been based on contested science, (exemplified by the recent controversy associated with the experimental assessment of GM maize NK603 (Academies nationales, 2012).[1] Some controversies have also confounded trait-specific effects and GM crop-related issues. Deploying herbicide-resistant varieties, for example, may have indirect beneficial or detrimental environmental effects irrespective of whether such varieties have been produced by GM technology or not (see Box 2 for further discussion). Any new tool or technology can cause unintended effects if used unwisely by adopting poor agronomic practice and it is vital to share lessons learned from the implementation of innovation. For the future, it is important not to generalise about the safety of conferred traits based on the technology used. Each new product must be assessed according to consistent risk assessment principles that examine the trait rather than the means by which the trait was conferred (see Chapter 4). It is also essential to ensure that benefit–risk is evaluated rather than focusing exclusively on risk (Box 2 and Chapter 4). In addition, the risk of not adopting any particular innovation should be assessed.

It is equally important to appreciate that there are other established techniques now emerging from advances in biotechnology for use in programmes of crop improvement. Collectively, all of the methodologies covered in the present report may be regarded as crop genetic improvement technologies. The mix of new tools coming within range is expanding rapidly and significant impact can be anticipated (Box 3).

For several of these New Breeding Techniques, the commercialised crop will be free of genes foreign to the species, which raises issues for detection and regulation as it will not be possible to discern the methodology by which the genetic improvements were achieved. The challenges for EU regulation of these New Breeding Techniques will be discussed later in Chapter 4.

1.5 Previous work by national academies of science in the EU

Prospects for the use of molecular biosciences in general, genetic modification in particular, and their contribution to agricultural innovation have been discussed previously by many of the constituent academies of EASAC. Their publications have documented where there is excellent relevant science to be nurtured and used. The academies have also highlighted where there are problems caused by the failure to take account of the accumulating scientific evidence in modernising and streamlining regulatory approaches to benefit–risk assessment. Concerns have repeatedly been raised that EU regulatory policy is not coherently supporting a strategy for the bioeconomy; some of the recent EASAC-academy publications are listed in Appendix 2.

Although no single technology can be regarded as a panacea (EGE, 2008; Bennett and Jennings, 2013), this

[1] This particular controversy relates to research published on GM maize NK603 where the study authors (Seralini et al., 2012) claimed a strong tumorigenic and toxic effect in rats. However, analysis of this research by the French academies, by EFSA (2012a) and the European Society of Toxicological Pathology (2013) raised many concerns about the initial publication in terms of its unclear objectives, inadequate disclosure of detail on study design, conduct and analysis, and small group sizes used. EFSA concluded that the study was of insufficient scientific quality for safety assessment. Criticisms of the original research publication, its methodology and reporting procedures have also been made by several other advisory bodies, for example the Federal Institute for Risk Assessment in Germany (2012) and the Italian Federation of Life Sciences (Federazione Italiana Scienze della Vita, 2013), and have been discussed in the scientific literature (see, for example, Butler, 2012). A comprehensive review of the literature on animal research, including long-term and multigenerational studies (Snell et al., 2012) had previously concluded that no such adverse effects were demonstrable. Recently, EFSA has made public its data and documents relating to the initial authorisation of GM maize NK 203 (Butler, 2013).

Box 2 Conceptual problems in the debate on impacts of GM technology

The environmental and socio-economic impacts of growing a crop – whether bred by genetic modification or not – are largely the result of agronomic practices and market issues. The interaction of these factors is often complex. The GM debate has suffered from several conceptual problems, illustrated here by discussion of the effects on the environment of the first generation of GM crops.

(1) Confusion of GM crop effects with effects caused by agricultural practices *per se*

Agricultural systems have profound impacts on all environmental resources, including biodiversity (Tilman et al., 2002). The use of GM crops causes changes in agricultural practice (such as a shift in the particular herbicides that are used on herbicide-tolerant crops and the replacement of insecticide applications by Bt crops) but the aims remain the same: the successful control of pests and weeds to ensure high crop yields. A recent review discussing evidence for the erosion of glyphosate efficacy emphasises the attribution in terms of poor crop management procedures, not GM-specific technology (Helander et al., 2012).The GM crop enabled the 'over-use' of the herbicide and imposed strong selection on weed populations. Because of the ideological controversy, studies on specific impacts of GM crops are often interpreted as a validation or rejection of the technology more generally. There is a conceptual flaw in this reasoning. The emergence of glyphosate-resistant weeds was no consequence of GM technology *per se* but the inappropriate reliance on a single herbicide for weed control that the GM crop facilitated.

(2) Lack of definition of 'harm'

The debate on safety has been complicated by the lack of a clear definition on how to assign a value to the effects of GM crops in the context of current agriculture. The interpretation of study results is often challenged by knowledge gaps about the natural variation occurring in any biological system and by a lack of comparison with 'conventional' agricultural practices that cause 'acceptable' environmental effects. To define what constitutes a 'harmful' effect first requires the characterisation of the environmental protection goals: those valued environmental resources that should not be harmed by GM crop cultivation or any other agricultural practice (Sanvido et al., 2012). It then has to be decided which changes to these protection goals should be regarded as relevant and, thus, represent unacceptable harm (Sanvido et al., 2012). Unless this is done, data that report any change in any measurement are open to interpretation.

(3) GM crops need to be incorporated in sustainable pest management systems

Because technology does not operate in a void, it is essential that suitable agronomic practices are in place to maximise the benefit that can be derived from agricultural innovation and to minimise potential adverse effects of novel technologies. Thus, novel agricultural technologies such as improved GM crop varieties do not negate the necessity for good agricultural practices but should be incorporated in integrated pest management and Integrated Weed Management programmes. When used incorrectly GM crops, like other agricultural technologies, can result in adverse environmental and agricultural impacts such as the development of resistant pests and weeds.

It is desirable for the emphasis of the debate to be shifted, from discussions of whether GM crops are good or bad, to exploration of the scientific and agricultural policies required to ensure that the potential value of GM technology from the EU perspective can be assessed within a concerted and integrated approach to food and biomass production.

previous academy work collectively makes a strong case that genetic improvement of crops – through breeding and genetic modification – should be part of an inclusive approach, which also embraces improved understanding of the benefits of ecological and agronomic management, manipulation and redesign (Pretty, 2008). Because of the complexities in the relationship between science and society, innovation in agriculture demands improved scientific understanding and good governance (Royal Society, 2009).

1.6 Objectives and scope of the present report

The present project builds on previous work by EASAC and on the mutual interests within member academies. We analyse the situation in countries outside the EU and the impact of EU policy on other countries as well as on the EU Member States – and elsewhere in Europe – and we identify various disconnects and inconsistencies in current EU policy. Our goal is to continue to focus constructive debate, founded on the evidence, across the

Box 3 Techniques that breeders use to create new plant varieties: crop genetic improvement technologies, encompassing GM and New Breeding Techniques

Transgenesis (GM): use of genetic transformation to transfer a gene (DNA coding region) from one organism to a different organism.

Cisgenesis: use of genetic transformation to transfer a gene to a plant of the same or closely related (inter-fertile) species.

Intragenesis: use of genetic transformation to insert a reorganised, full or partial coding region of a gene derived from the same species (usually combined with a promoter or terminator from another gene of the same species).

Targeted mutagenesis: specific mutation mediated by, for example, zinc-finger nuclease (may be stable, ZFN3, or only transient, ZFN1 and 2, integration of DNA according to technique) or TALEN (Transcription Activator-Like Effector Nuclease) technology.

Other transient introduction of recombinant DNA: for example, oligonucleotide-directed mutagenesis and agro-infiltration. The end products can be similar to, and indistinguishable from, plants derived through conventional plant breeding.

Other New Breeding Techniques: these include RNA-induced DNA methylation (gene silencing) and reverse breeding, where intermediate products are genetically modified but end products are indistinguishable from plants obtained through conventional breeding. Grafting a non-genetically modified scion onto a genetically modified rootstock results in a chimeric plant where only the lower part carries the genetic transformation.

See the following references for further detail of techniques: Tait and Barker, 2011; Grushkin, 2012; Lusser et al., 2012a, b; Mba et al., 2012; Podevin et al., 2012; Waltz, 2012.

wider scientific and policy communities, as well as with the public at large. The primary purpose is to explore the implications for EU policy-makers of alternative strategic choices in using the tools available – the crop genetic improvement technologies – for delivering sustainable agriculture. In this context, economic sustainability and environmental sustainability are both crucial. If strategic coherence is to be achieved, it is vital for the EU policy-making institutions to combine optimally their dual roles and responsibilities for proportionate regulation and enabling innovation in support of the bioeconomy.

We take a multi-dimensional approach to evaluating the evidence:

(1) Comparing what is happening in other economies worldwide who have taken a different path by their decision to adopt GM crops more actively. Our analysis examines different facets from the reported socio-economic and environmental impacts and the implications for science and innovation in the comparator countries (Chapter 2 and Appendix 3). The different strategic decisions on agriculture in other countries may, in turn, have consequences for EU policy, not just in terms of the burgeoning global competition but also by constraining EU policy choices. For example, the EU desire to import non-GM crop food/feed may be progressively limited by the declining availability of non-GM crops in the major exporting nations in the Americas and Asia.

(2) Ascertaining the implications of EU practices and perspectives on the various applications of crop genetic improvement technologies in countries in Africa. In particular, in partnership with our academy colleagues in the Network of African Science Academies (NASAC), we seek to evaluate how previous EU policy debates and decisions pertaining to GM crops affect policy-makers and other opinion-leaders in African countries (Chapter 3 and Appendix 5). NASAC has already been active in supporting discussion of the issues for agriculture, environmental change and biotechnology[2]. NASAC–EASAC compilation of the historical evidence together with analysis of contemporary views and future trajectories for agricultural innovation and the science base in African countries may, in turn, help to delineate a new evidence stream to inform future EU policy decisions.

(3) Bringing the international evidence together with analysis of the present situation in the EU, we discuss whether the EU regulatory environment governing crop genetic improvement technologies could be enhanced by re-affirming the principles of evidence-based policy (Chapters 4 and 5). A new approach in this regard – regulating traits and the product rather than the technology – is likely to have far-reaching consequences, for food security, sustainable agriculture, environmental quality, scientific endeavour, European competitiveness and EU–global relationships. Our primary focus is on the science and technology rather than legal matters; we aim to demonstrate how the available scientific evidence can be better used to inform policy options.

[2] For example in a conference in 2010 organised jointly with the Royal Netherlands Academy of Arts and Sciences on 'Impact of adaptation to climate change in relation to food security in Africa'. The proceedings of the conference are available at http://www.nasaconline.org/network-resources/cat_view/7-network-documents?start=5.

The EU agricultural biotechnology debate is complex and polarised (Butschi et al., 2009; Tait and Barker, 2011; van Montagu, 2011), with multiple implications for other policy associated with the environment, health, international development, research, innovation and enterprise. It is not our intention to duplicate the detailed analysis that has already been well reported by others, but we will cite it when appropriate. We think our report is timely. Although it is true that the value of agricultural innovation has been repeatedly discussed over the past three decades, and our messages may seem familiar in some respects, we judge that it is vitally important to continue to draw attention to the potential of the biosciences for crop improvement. This is particularly so as we begin to understand better the consequences of EU policy decisions in the global context, and now that food security is becoming a much higher political priority for EU citizens. There is room for optimism that the global challenges facing food and farming can be addressed and overcome. This is not least because the natural sciences continue to provide new knowledge to stimulate innovation and inform policy options (Bennett and Jennings, 2013) and because the European Commission is reaffirming its commitment to catalyse discussion and action through initiatives such as the European Innovation Partnership in Agriculture.

2 International comparison of policy choices and GM experience

Summary of emerging points from Chapter 2

- Many countries in the Americas and Asia are actively adopting GM crops. Agricultural innovation is becoming an important part of the economy in many countries outside the EU. In this chapter, case studies are provided from different countries to exemplify particular points relating to impact, research and development (R&D) and regulation.
- There is now a significant volume of information from environmental and socio-economic indicators to characterise the impact of the first generation of GM crops, revealing a range of benefits. Therefore, it is critically important to ensure that the adoption of GM crops is given due consideration, based on the scientific evidence, within well-characterised good agricultural practice, and alongside attention to other multiple societal challenges associated with marginalisation and inequity. According to the aggregate evidence, GM has no greater adverse impact than any other technology used in plant breeding.
- Considerable experience is being gained in developing workable GM crop regulatory frameworks that also act to encourage innovation and support significant growth in research.
- There is an enhanced role possible for many academies of science worldwide in using the available scientific evidence to advise on the options for policy-makers. There would also be great value in ensuring better global coordination of such advice.

2.1 Introduction

GM crops were planted commercially for the first time in 1996, on a surface area of 1.7 million hectares. By 2012, the total area cultivated with GM crops had risen to over 170 million hectares and, significantly, over half of this production is now accounted for by developing countries (James, 2012; and see Chapter 1).

Different strategic decisions taken by other countries are expected to have consequences for EU policy, not just in terms of burgeoning global competition, but also by constraining EU policy choices. The objective of this chapter is briefly to describe emerging global trends in terms of policies regarding food production, trade and investment in agricultural R&D over the past decade or so, and to highlight some of the likely implications of these trends for the EU in the medium term. The socio-economic and environmental impact and regulatory framework related to the adoption of GM crops in several comparator countries who have taken a different path by their decision to adopt GM crops more actively will be analysed. In this chapter we highlight specific aspects in the different countries, selected to illustrate particular key issues for impact, innovation and regulation. Additional background information on the comparator countries, with respect to status of adoption of GM crops, regulatory systems, socio-economic impacts and trends in agricultural research is provided in Appendix 3, whereas Appendix 4 briefly describes methodological considerations in assessing the impact of GM crops. An analysis of selected African countries is provided in Chapter 3 and Appendix 5.

The comparator countries that have been chosen for a more in-depth analysis in the present chapter are Argentina, Brazil, India, Australia and Canada. The reasons for this choice are as follows.

1. These counties were early adopters of GM technology and each now grows GM crops on a large scale (more than one million hectares each).

2. These economies account for a major portion of global grains and oilseed production, and play a significant role in the global trade of these commodities.

3. The emerging economies of Argentina, Brazil and India have also established, to varying degrees, important research programmes for the development of GM crops suited to local agronomic conditions and market needs. These are funded by both the public and the private sectors and hence these countries are set to become increasingly important technology providers in the short- to mid-term. In 2011 Brazil approved production of a GM bean variety, the first authorised GM crop developed exclusively with public funding. India has also developed a GM crop (GM aubergine) which addresses important national agricultural constraints (although it has yet to approve it due to political and civil society opposition). In addition, these countries have developed the institutional requirements needed rapidly to adapt foreign GM technology to suit local agronomic conditions and needs.

4. Australia will also be considered in this review, because the policies pertaining to food production, science and innovation in agriculture of this country are very mindful of strategic decisions taken by developing countries with regards to the uptake of GM crops. In addition, the Australian experience with

Bt cotton provides a good example of the value of incorporating insect-resistant GM crops in integrated pest management systems for more effective and sustainable control of pests.

5. Canada has been selected on the basis of its regulatory system for Plants with New Traits, which include the products of genetic modification. This system focuses on regulating the product rather than the breeding process by which such product was developed and it is this aspect that we discuss, rather than some of the other impacts for Canada.

The USA, the leading technology developer and an early adopter of GM crops, will not be specifically considered in this chapter although it should be emphasised that there have been historically divergent approaches between the EU and USA about the introduction and marketing of GM foods and seeds (Lynch and Vogel, 2001). Many other studies have focused on the USA (Fernandez-Cornejo and Caswell, 2006; Bonny, 2008; Fuglie et al., 2011; O'Donoghue et al., 2011; Owen et al., 2011; McHughen and Smyth, 2012; United States Department of Agriculture, 2012). In the comprehensive assessment by the US national academies (National Research Council, 2010) of how GM crops are affecting US farmers[3], substantial economic and environmental benefits (lower production costs, fewer pest problems, reduced use of pesticides, better yields) were found, compared with conventional crops, if GM approaches were properly integrated with other proven agronomic practices for weed and insect management. It is also worth noting that the USA is continuing to consider how best to support its science and innovation in agricultural biotechnology. For example, in its launch of the National Bioeconomy Blueprint (The White House, 2012), the USA is reinforcing five strategic objectives: to strengthen R&D, advance from laboratory to market, reduce regulatory burden, develop the workforce and foster partnerships[4]. The US President's Council of Advisers on Science and Technology has recently submitted its report to the President on Agricultural Preparedness and the Agricultural Research Enterprise. In addition to recommending continuing research investment, the Council of Advisers drew attention to the need for an internal review of federal regulatory policy to promote clarity[5].

2.2 Emerging trends

The different strategic decisions on agriculture in other countries are likely to have consequences for EU policy, in terms of agricultural production, international trade and investment in agricultural research and development.

2.2.1 Agricultural production

GM is a plant breeding technology that, in effect, accelerates the breeding process by overcoming some of the limitations of conventional breeding techniques. Policies that restrict the use of this technology in the EU will probably affect food production by effectively limiting the technology options available to overcome the challenge of increasing agricultural productivity. These policies may impact the level of competitiveness of the EU as an exporter of food, biomass and non-food plant products, and increase dependency on imports to meet demand. These aspects have been reviewed extensively before and will not be considered further in this review (von Witze and Noleppa, 2010; Chidambaram, 2011; EPSO, 2011; Dixelius et al., 2012; see also Chapter 4).

2.2.2 International trade

Alternative agricultural and technology policies adopted in major commodity export countries outside the EU, and the stance of the EU on imports of GM crops, also have an impact on international trade. The USA, Australia, Canada and the four emerging economies of Argentina, Brazil, China and India account for a major portion of global grains and oilseed production and play a significant role in the global trade of these commodities. These countries have also all adopted GM crops, and in 2012 they collectively planted over 150 million hectares of GM crops (over 90% of the global total; James, 2012).

The EU, on the other hand, is a key importer of soybeans, maize, wheat and rice (GM rice is a product that is in the 'pipeline', with GM wheat further into the future). Labelling and segregation requirements add to the costs of imports and hence increase food prices. In addition, the EU's demand to source non-GM food or feed imports may be progressively limited by declining availability and/or increased costs of conventional crops in major commodity exporting nations.

The number of commercialised GM events is predicted to rise from approximately 40 released so far, to over 120 by 2015, with a diversification in both crop species and traits engineered (Stein and Rodriguez-Cerezo, 2010; and see Chapter 4). This will involve both a diversification of crop species and the selected traits (Stein and Rodriguez-Cerezo, 2010). Trade-related problems are therefore likely to be exacerbated in the future. The implications for international trade of diverging and asynchronous

[3] Introduced in 1996 in the USA, in 2009 GM crops accounted for 80–90% of soybean, maize and cotton grown.
[4] For example, one key partnership exemplified in the Blueprint for the USA–UK is to design and engineer agricultural systems to maintain or increase crop yields with minimal input of nitrogen fertilisers.
[5] See http://www.whitehouse.gov/administration/eop/ostp/pcast.

approval patterns for GM crops in exporting and importing countries have been reviewed in the scientific literature and will not be considered further in this chapter (see Stein and Rodríguez-Cerezo, 2009, 2010).

The predicted future trends in global population are also likely to shift the balance in international trade relations. Most of the population growth is expected to occur in Sub-Saharan African countries and in Asia[6] and as a result food demand will increase considerably. Although this represents a huge humanitarian challenge, it also signifies a very important market opportunity for commodity exporting countries (see the section on Australia in Appendix 3). One implication of the rise in Asian food demand may be that the EU will have to face increasing competition with other countries in agricultural commodity markets.

2.2.3 Global trends in agricultural research and development

The past couple of decades have witnessed a shift in the global distribution of investment in science and innovation, particularly pertaining to agricultural research. Although traditionally the USA, Europe and Japan have led in terms of investment in R&D, their dominance is increasingly challenged by emerging economies (UNESCO, 2010; ASTI, 2012). A growing number of public and private research hubs are being established in developing countries, which are emerging as key technology providers (Ruane, 2013).

Between 2000 and 2008 public investment in research and development (in all areas of science and technology) in China dramatically increased from about 90 billion yuan (US$10.8 billion) to over 460 billion yuan (US$66.5 billion) at an average annual growth rate of 23% (UNESCO, 2010). In the same period, public spending in agricultural research doubled[7]. In India, one of the fastest-growing economies in the world, strong government commitment has also resulted in a near doubling of public investment in agricultural R&D since the mid-1990s. After China and India, Brazil ranks third in terms of agricultural investment in developing countries (ASTI, 2012).

This trend is even clearer when the contribution of the private sector to science and technology is considered (UNESCO, 2010; Brookes and Barfoot, 2012; Dixelius et al., 2012; Pray, 2012). In 2006, 16% of China's total spending on agricultural R&D came from private enterprises, up from less than 3% in 1995 (ASTI, 2012). Similarly, private investment in agricultural R&D has increased fivefold in India since the mid-1990s (ASTI, 2012). Private-sector firms have become major players in developing new innovations for agriculture worldwide (Pray, 2012).

Some of the factors driving companies to invest in agricultural research include the emergence of scientific advances, the strengthening of intellectual property rights, the global expansion of markets for agricultural inputs (including seeds), and changing government regulations. Average annual growth in sales of crop seed and biotechnology traits between 1994 and 2009 was estimated at 6.9%, and in 2006 the market sales in the sector were worth US$20 billion (Fuglie et al., 2011). The rapid growth of sales of GM products in developing countries has attracted private sector investment in research to the countries where farmers are using the technology. Private-sector R&D expenditures in input industries increased by more than 40% in (inflation-adjusted) US dollars over the period 1994–2010 (Fuglie et al., 2011). The most R&D-intensive sector is crop biotechnology. In 2009, research intensity was over 10% of the value of annual seed sales (Fuglie et al., 2011).

Some examples of products developed to address the needs of emerging economies include GM white maize in South Africa and hundreds of Bt cotton hybrids developed by the private sector to suit local agricultural conditions in India (da Silveira and Borges, 2005; Pray, 2012; see country sections below and Chapter 3). Investment in agricultural research to develop GM products for developing countries as public–private partnerships is also significant[8].

In the EU this trend is reversed. The misuse of the precautionary principle has led to restrictive legislation and both a political and market mistrust of genetically modified organisms (GMOs). This has had a profound chilling effect on both public and private investment for European agricultural research (see Chapter 4). This trend is also reflected in the steady decrease in the number of field trials of GM crops in Europe: the number of applications submitted in 2012 were 44 (30 in Spain), down from 51 in 2011, 83 in 2010, and 113 in 2009[9].

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[6] During 2011–2100, six countries are expected to account for half of the world's projected population increase: India, Nigeria, the USA, the Democratic Republic of Congo, the United Republic of Tanzania and Uganda, listed according to the size of their contribution to global population growth. Source: World Population Prospects – The 2010 Revision, prepared by the Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat. http://esa.un.org/unpd/wpp/Documentation/pdf/WPP2010_Highlights.pdf.

[7] China has the world's largest and most decentralised public agricultural research and development system. It employs over 40,000 researchers in more than 1,000 research agencies at the national, provincial and prefectural levels (Chen et al., 2012).

[8] For a list of PPP for R&D projects of GM crops see http://www.syngentafoundation.org/index.cfm?pageID=745&country=&sortitem=projectType_ID_FK&projectType_ID_FK=6

[9] http://gmoinfo.jrc.ec.europa.eu/gmp_browse.aspx.

By comparison, Argentina alone performed 72 field trials in 2011[10].

2.3 Reported impacts and the implications for science, innovation and regulation in comparator countries

2.3.1 Reported impact of GM herbicide-tolerant soybean in Argentina

Cumulative gross benefits of adopting GM crops for Argentina have been estimated at over US$72 million, with most of the reported benefits accounted for by soybean production (US$65 million for herbicide-tolerant soybeans, US$5 million for GM maize and just under US$2 million for insect-resistant and herbicide-tolerant GM cotton; Trigo, 2011). Argentina's capacity to act as an 'early adopter' was reported to be critical because it allowed the country to benefit from initial low levels of competition in international markets and higher commodity prices (Trigo, 2011).

The expansion of GM soybean production was accompanied by profound changes in the Argentinean economy that favoured the geographical concentration of agricultural production and development of large-scale operations. Soybean production expanded as a monoculture, or as a wheat–soybean double-cropping system (Bindraban et al., 2005). Bulk export of soybeans also led to an increase of farm size due to the financial benefits from economies of scale (Manuel-Navarrete et al., 2009). These factors promoted input-oriented and process-oriented practices, with a significant increase in the level of mechanisation (Bindraban et al., 2009; Manuel-Navarrete et al., 2009). The adoption of GM soybean fitted these systems well and therefore contributed to the expanded scale of production even though this is not essential for beneficial deployment of the technology (for example, in Brazil, this increase in farm sizes took place before the adoption of GM soybean, see Appendix 3). About 50% of the soybean crop sown in the 2002/2003 season was planted in areas that were not cultivated in 1998 (LART–FAUBA, 2004). This raised concerns about the potential adverse impact on fragile ecosystems in Argentina if there was a gradual expansion of soybean production (Bindraban, 2009; Trigo, 2011). Extensive monoculture has also raised concerns about the sustainability of this agronomic practice (Bindraban et al., 2009; Trigo, 2011).

There is a consensus that herbicide-tolerant GM technology does not have a significant impact on yield, because differences reported are largely accounted for by differences in the specific genetic background into which the GM trait was introduced, and by differences in agro-climatic conditions (da Silveira and Borges 2005; Smale et al., 2006; Bindraban et al., 2009).

The direct environmental impact of growing GM soybeans relates mostly to changes in weed control practices. Compared with many other herbicides, the eco-toxicity of glyphosate is lower with shorter residual effects in soil and water. A further benefit of the technology is the ability to adopt no-till farming practices which prevent soil erosion, loss of water and nutrients, and reduced fuel consumption (Qaim and Traxler, 2005; Kleter et al., 2007, Bindraban et al., 2009; Brookes and Barfoot, 2012; Trigo, 2011)[11].

Negative environmental impacts have also been reported. These include an increase in herbicide use (because application rates are generally higher compared with conventional counterparts) for herbicide-tolerant soybean and in no-till systems independently of whether the crop grown is GM or conventional (Bindraban et al., 2009; Trigo, 2011, Brookes and Barfoot, 2012). The environmental impact of herbicide-tolerant soybean has been estimated to be higher than that of conventional soybean in one study (Bindraban et al., 2009) and lower in separate studies (Brookes and Barfoot, 2006, 2012). The difference in the conclusions can be accounted for by different sources of data and the fact that the former study focused on the main soybean cropping areas of Argentina where a higher level of inputs tend to be used rather than on the country as a whole (Bindraban, 2009).

Extensive glyphosate use has also resulted in the emergence of glyphosate-resistant weeds, a factor that threatens to erode the benefits of herbicide-tolerant GM technology (Cerdeira et al., 2006, 2011; Christoffoleti et al., 2008; Powles, 2008; Bindraban et al., 2009). Farmers tend to increase glyphosate applications to control herbicide-resistant weeds, which exacerbates the problem. A further negative consequence of the high level of production of soybean in Argentina (albeit not directly linked to GM technology because it would occur with any crop) is the loss of phosphate from the soil, estimated to amount to 14 million tons between 1996 and 2010 (Trigo, 2011)[12].

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[10] http://64.76.123.202/site/agregado_de_valor/biotecnologia/50-EVALUACIONES/___historica/_archivos/liberaciones_ogm_2011.pdf.

[11] Glyphosate replaced imidazolines for broad-leafed weeds and soil-incorporated triazines for controlling grass weeds (although these are still used to address residual weed problems in GM plantations, whereas glyphosate is also used in conventional plantations as a pre-emergence herbicide; Kleter et al., 2007).

[12] GM plants able to metabolise phosphite as a source of phosphorus are currently being developed (López-Arredundo and Herrera-Estrella, 2012).

It has been suggested that corrective policies for food production and suitable R&D policies to improve existing technologies need to be implemented as well as adoption of good agricultural practices (i.e. farm zoning, use of non-chemical weed control methods, crop rotations and nutrient replacement) (Behrens et al., 2007). The need for strategies to provide long-term sustainable productivity has also been suggested (Powles, 2008). The EASAC view and that of many other expert groups is that these challenges are not in any way unique to deployment of GM crops; they apply to crop production systems using conventional varieties and essentially relate to the problems associated with crop monocultures as well as the sole reliance on crop protection compounds (such as specific herbicides) with a single mode of action.

2.3.2 Socio-economic impact of Bt cotton in India

The only GM crop that India has commercialised is Bt cotton, first officially approved in 2002 after the completion of comprehensive safety studies[13]. Since 2007 (when it overtook the USA), India has been the country with the greatest area of cotton cultivation (12 million hectares). India is also the second greatest producer of cotton lint in the world (FAOSTATS, http://faostat.fao.org/site/339/default.aspx). Production of cotton lint in India more than tripled between 2002 and 2010. In 2012 the area under GM cotton was 10.8 million hectares (James, 2012).

Scientific studies assessing the performance of Bt cotton in India report overall a positive effect of the technology. An analysis of a dataset collected between 2002 and 2008 shows that the use of Bt cotton has resulted in a 24% increase in cotton yield per acre through reduced pest damage and a 50% gain in cotton profit among smallholders (Kathage and Qaim, 2012). The study concludes that Bt cotton has delivered sustainable benefits and contributes to positive economic and social development in India (Kathage and Qaim, 2012). Bt cotton is reported to have contributed 19% of total yield growth in nine Indian cotton-producing states from 1975 to 2009 (the use of fertilisers and of hybrid seeds being other significant variables; Gruère and Sun, 2012). In addition, Bt cotton also provides farmers with indirect economic benefits, such as time and labour savings resulting from the reduced number of pesticide applications required. The time saved can be devoted to other income-generating activities (Subramanian and Qaim, 2009).

The positive performance of Bt cotton was confirmed by a meta-analysis of the economic and agronomic performance of GM crops worldwide using a variety of approaches (Areal et al, 2013). Bt cotton was found to be the most profitable crop followed by Bt maize (Areal et al., 2013). GM crops performed best in developing countries, probably because of the lack of alternative efficient and affordable pest management practices (Brookes and Barfoot, 2009, 2012; Carpenter, 2010, 2011; Finger et al., 2011; Areal et al., 2013).

The environmental and human health benefits from adopting Bt cotton have also been extensively documented. These are mostly a function of the decreased use of chemical pesticides required during cotton production (Kouser and Qaim, 2011; Stone, 2011; Krishna and Qaim, 2012).

Nonetheless, despite the nearly universal adoption of the Bt cotton in India and the growing body of scientific evidence in support of the technology, the success of Bt cotton in India continues to be a highly controversial topic (Herring, 2006, 2008a, b; Stone, 2011; Herring and Rao, 2012). Much of this controversy revolves around ethical arguments that form part of a global polemic on use of GM crops in food production. Concerns cited include control by multinationals of the agricultural sector and fears over human health and the environment. Opposition has largely been driven by a coalition of non-governmental organisations (NGOs) connected to international advocacy organisations (Herring 2006, 2008a, b).

Among other allegations, Bt cotton is linked to widespread agronomic and crop failures and of being the main reason for a resurgence of farmers' suicides in India. Farmers' suicides in India are a serious problem that pre-dates the adoption of Bt cotton. A study exploring the link between the cultivation of Bt cotton and farmers' suicides established lack of supporting evidence for a resurgence of suicides linked to the adoption of Bt cotton (Gruère et al., 2008). The authors note, however, that the performance of Bt cotton, although positive on average, varied in different locations and seasons. Crop failures were considered a consequence of unfavourable climatic conditions, and these failures were compounded by low market prices for cotton, inappropriate farming practices, misinformation about the new technology and the widespread use of early Bt varieties that were not adapted for all locations and farming practices (Gruère et al., 2008, 2010). Institutional problems, such as weak agricultural extension services, lack of irrigation in drought-prone areas, the absence or failure of agricultural credit and financing systems, and the high prevalence of adulterated and fake seeds and inputs further exacerbated the situation. Because there are reports attesting to the beneficial effects of cultivating Bt cotton and the fact that the factors determining farmers' suicides have existed before the introduction of Bt cotton, the proof linking the two remains weak and controversial (Gruere and Sun, 2012).

[13] http://www.envfor.nic.in/divisions/csurv/geac/bgnote.pdf.

Very similar conclusions were reached by a study assessing the causes of suicides in the 1997–1998 growing season (4 years before the official adoption of Bt cotton in India; Reddy and Rao, 1998). The authors identified as a common feature of the agricultural landscape a sharp increase in the proportion of small farms: 80% of the holdings were below 5 acres, and half of the farms were smaller than 2.5 acres[14]. Factors that contribute to the fragmentation of the land include population growth, lack of opportunities outside agriculture, a decline in caste occupations and the breakdown of the joint family system[15] (Reddy and Rao, 1998).

Because traditional crops fetch low prices, farmers in small holdings tended to move to higher value cash crops, such as cotton, although these crops may not have been suitable for the soil types and environmental conditions of the region. Small farms typically face more severe limitations of capital resources and credit in the process of adopting new agricultural technologies, such as seeds, inputs, irrigation and farm machinery[16]. The study lists the same causes as contributing factors in a decline in return-cost ratios leading the farming community into a debt trap: lack of fair credit systems, volatility in cotton prices, lack of provision of adequate agricultural advice, unsuitable and unsustainable farming practices, and adulterated seeds and inputs (Reddy and Rao, 1998). The emergence of very small holdings, declining employment opportunities in rural areas and the neglect of semi-arid region and dry-land agriculture are interpreted as symptomatic of a deeper crisis of the Indian agricultural sector that requires significant policy interventions and investment by the government for rectification (Reddy and Rao, 1998).

The policy recommendations of the studies reviewed are overwhelmingly in agreement: policies directed at improving the overall economic development of rural areas are a requisite for ensuring that the potential benefits of GM crops are fully realised (Gruère et al., 2008, 2010; Subramanian and Qaim, 2009; Stone, 2011; Herring and Rao, 2012). These include policies aimed at improvements in infrastructure and access to education and financial markets.

The Bt cotton controversy has had significant effects on ongoing research programmes, and on the commercialisation of products from research. According to the Indian Department of Biotechnology, over 70 GM crops (70% of which are developed by the public sector) are at various stages in the regulatory process and pending approval from the Genetic Engineering Appraisal Committee (GEAC) (Jayaraman, 2012). The most significant casualty of the system is arguably Bt brinjal (aubergine); although the crop received commercial approval by GEAC in late 2009, it was subsequently banned by the Indian Government in 2010 in the wake of fierce opposition by some NGOs. This situation has not yet been resolved (Padmanaban, 2009; Bagla, 2010; Shelton, 2010; Bandopadhyay et al., 2012; Jayaraman, 2012; Laursen, 2012; Pingali, 2012; Kudlu and Stone, 2013).

Ongoing scrutiny of the performance of GM crops relative to their conventionally bred counterparts and the endorsement of public debates that incorporate the social and cultural dimensions of the deployment of new technologies are essential to determine the contribution that a new technology can make to increasing agricultural productivity and sustainability. These debates are not, however, a substitute for reforms tackling underlying problems with existing agricultural systems, which cannot be addressed by any specific plant breeding technology *per se*. EASAC believes it is vital for the emphasis of the debate on GM crops to be shifted to a primary focus on the policies required to ensure that the potential value of novel plant breeding technologies is realised.

2.3.3 Bt cotton in Australia: a case history

Australia has approved GM cotton and GM oilseed rape for cultivation. GM cotton has been grown since 1996 and now makes up around 95% of Australia's cotton crop (Australian Department Agriculture, Fisheries and Forestry, 2012).

Bt cotton was deployed in Australia primarily to control *Helicoverpa armigera* and *H. punctigera*, major pests for the cotton industry. *H. armigera* has a high capacity to develop resistance rapidly to many classes of insecticides. By the mid-1990s, up to 14 applications of insecticides were required to control this pest in Australia (Forrester et al., 1993; Downes and Mahon, 2012). The first Bt cotton released was INGARD® (known as Bollgard elsewhere). INGARD® produces the Cry1Ac protein from *Bacillus thuringiensis*, and although this protein is the most toxic of the insecticidal proteins tested against

[14] These figures are in agreement with more recent estimates. Most landholdings are small: 82% were classified as small scale in 2006; and farms less than two hectares occupied 40% of India's agricultural land. Close to 60% of India's workforce is employed in agriculture, according to the 2011 census (Government of India, 2011).

[15] Under the traditional system in India, the entire family, paternal grandparents and their children with their families, stay under a single roof. Each member of the family shares the household/farm chores and the system is linked to inheritance patterns and property institutions.

[16] Although Bt cotton benefits all farmers regardless of the size of the holdings, a study on the effects of Bt cotton adoption at the village level (Subramanian and Qaim, 2009) recorded a correlation between the size of farms and the degree to which farmers benefitted from adopting GM seeds. This correlation is also explained by the generally better economic endowment of larger farms, rather than by inherent scale effects of the technology.

H. armigera, it is nearly 30 times less toxic to *H. armigera* than to a key target of transgenic cotton in the USA, *Heliothis virescens*. Overall, the average production of pupae throughout the growing period of INGARD® cotton was 60% of that with conventional cotton (Baker et al., 2008). For this reason INGARD® was released as a component of an integrated pest management system, and treated as an interim product.

The resistance management plan for Ingard cotton in Australia was initially developed in 1996 by the Monsanto Australia Limited Cotton Team in consultation with the Transgenic and Insecticide Management Strategy Committee of the Australian Cotton Growers Research Association (now Cotton Australia). Two independent programmes to monitor the development of resistance in insect populations in the field were established.

The resistance management plan included the following components in 1996: restricting Bt cotton to 10% of the area of cotton grown on a farm (the cap was increased to 30% in subsequent years); including a refuge for susceptible insects (pigeon pea was recommended as the refuge option); restricting sowing to a defined period to limit the number of generations over which insects were exposed to the toxin; required use of synthetic sprays late in the season to control insect populations; and at the end of the season it was mandatory to cultivate the soil in areas with INGARD® cotton to increase mortality rates among potentially resistant pupae (Downes and Mahon, 2012).

By the time INGARD® was replaced by Bollgard II® (which in addition to *Cry1Ac* also expresses the *Cry2Ab* gene) in 2004, the frequency of resistant alleles to Cry1Ac was still very rare in *H. armigera*. The cap on the area that could be used for Bt-cotton was removed allowing for up to 95% of the farm to be planted with Bollgard II® if the smallest refuge option (5%, pigeon pea) was used. Use of Bollgard II® still requires a need to pupae-bust[17], plant within defined dates, and control volunteer plants (Downes et al., 2010). A third generation Bt cotton is expected to be released around 2016: Genuity Bollgard III®. This version will retain Cry1Ac/Cry2Ab and include Vip3A[1], another protein that can be used further to delay the development of resistance of pests in the field (Mahon et al., 2012).

Bollgard II® accounts for up to 95% of cotton planted in Australia and its adoption has resulted in a decrease of 85% in the amount of conventional insecticides used during cotton production (these are mostly used to control secondary non-lepidopteran pests; Knox et al., 2006; Constable et al., 2011; Downes and Mahon, 2012).

The Australian experience with Bt cotton is illustrative of the fact that the adoption of insect-tolerant GM crops within the context that maximises the long-term sustainability of the technology is a knowledge-intensive process. Success of the GM technology has been built on a pre-emptive resistance management strategy. Crops engineered for resistance to pests are ideal components of integrated pest management systems, rather than isolated stand-alone solutions.

2.3.4 Trends in GM research in Brazil

In 2012 Brazil planted over 36 million hectares of GM soybean, maize and cotton (James, 2012). Brazil is the second largest (by volume) exporter of soybeans in the world after the USA; the crop is substantially of GM origin. Soybean production in Brazil increased from 23 million tonnes in 1996 to 69 million tonnes in 2010, and in 2010 Brazilian soybeans exports exceeded US$11 billion (FAOSTATS).

One of the consequences of the economic benefits accrued from adopting GM crops in Brazil (see Appendix 3 for details) has been a very strong government commitment and investment in agricultural biotechnology research[18]. Agricultural R&D in Brazil is largely government-funded. Brazil ranks third in the developing world[19] in terms of total public agricultural R&D investments after China and India; however, it spends about 20 times more per agricultural worker than these countries (Beintema et al., 2010).

One of the largest public sector tropical agriculture R&D organisations in the world, Embrapa (Empresa Brasileira de Pesquisa Agropecuária, the Brazilian Enterprise for Agricultural Research) has an annual R&D budget of over US$1 billion, and more than 2,300 researchers in 42 centres located around Brazil. In addition to Embrapa,

[17] Pupae-bust, the full surface cultivation to a depth of 10 cm of land previously under cotton cultivation, is an important part of resistance management. Pupae of *Helicoverpa* species that overwinter in the soil have a high risk of carrying insecticide resistance into the next season. Disturbing the emergence tunnels and exposing them to predators increases the number of pupae that fail to emerge or that can be eaten or parasitised (http://www.greenmountpress.com.au/cottongrower/Back%20issues/286oncot07/21_Pupae.pdf).

[18] After a period of stable or declining expenditure levels, renewed government commitment in agricultural R&D has resulted in a surge of investment: public spending on agricultural research in 2009 was 28% higher than in 2008 (Beintema et al., 2010). Training and capacity building initiatives also received significant government investment (and international loans), and as a result 75% of Embrapa's researchers were trained to the PhD level in 2008, up from 3% in 1976, indicating a rapid expansion of the research base (Beintema et al., 2010).

[19] Brazil investment in R&D constitutes 60% investment of Latin American countries (UNESCO Science Report, 2010). Brazil's leadership in publications on biotechnology is also unrivalled: the country accounts for 49% of articles for Latin American countries, many of which the result of international research collaborations (UNESCO Science Report, 2010).

a network of agricultural research agencies in 17 of the country's 26 states also performs agricultural research in Brazil, with a focus on applied research addressing state priorities (Beintema et al., 2010).

Embrapa's research is organised under the strategic framework MC1 (Macroprograma 1 da Embrapa - Grandes Desafios Nacionais[20]). MC1 projects with a component of GM technology include the following:

- Forests for energy production is set to reduce the deficit in raw materials from forests for the conversion of biomass into energy by developing seed and clonal material adapted to different agro-ecological zones. One of the collaborating companies recently signed an agreement with Embrapa. The first project to be executed under this agreement will incorporate an aluminium-tolerance gene owned by Embrapa into eucalyptus germplasm to enhance yields in areas affected by aluminium toxicity in the soil.

- Sustainable production of sugarcane for energy generation. This integrated project comprises five research themes with the aim to develop sustainable production systems for sugarcane. Research activities will take place in the major sugarcane producing states and in those with potential for sugarcane cultivation. Objectives include development of drought-tolerant GM sugarcane, GM sugarcane with resistance to the giant sugarcane borer and optimisation of biological nitrogen fixation systems.

- Technologies for biodiesel production. This project aims to develop new varieties of castor bean, sunflower, soybean, canola and oil palm to supply the demand of vegetable oils in Brazil. Emphasis will be placed on nutrient uptake and resistance to pests and diseases.

Although many Embrapa research centres are engaged in GM research, the Embrapa National Centre of Genetic Resources and Biotechnology (CENARGEN[21]), was specifically established to promote research, development and innovation in genetic resources for the sustainability of Brazilian agriculture. The main lines of research in CENARGEN comprise bioactive substances, genetic improvement of cassava, genetic improvement of peanuts, biotic and abiotic stress, and transgenesis, intellectual property rights and biosafety.

CENARGA projects under '*Transgenesis, Intellectual Property Rights and Biosafety*' include the development of the following biotech products:

- The *CAHB12* gene from coffee has been used to transfer increased drought tolerance to soybean, cotton, rice and wheat (da Cruz et al., 2007).

- GM plants with resistance to pathogenic fungi (Dias et al., 2006; Santos et al., 2009; Tinoco et al., 2010).

- GM sugarcane with resistance to the sugarcane giant borer, and with tolerance to drought (Craveiro et al., 2010; Cheavegatti-Gianotto et al., 2011).

- Insect-resistant GM cotton (Oliveira et al., 2011).

- GM coffee with resistance to the coffee borer beetle (Barbosa et al., 2010), and to root nematodes (Albuquerque et al., 2010).

- Biofortified GM crops (Nunes et al., 2009).

- Development of biopharmaceuticals in plants (Cunha et al., 2011a, b).

- Plant-based protein production biofactories for the expression of genes from spider for silk production (Teulé et al., 2009; Vianna et al., 2011).

Brazil is therefore posed to become a major agricultural technology provider in the medium-term, and to increase the importance of its role in the international trade in commodities.

2.3.5 The Canadian regulatory system for plants with novel traits

Plants in Canada are regulated on the basis of the traits expressed and not on the basis of the method used to introduce the traits[22]. Plants with novel traits (PNTs) may be produced by conventional breeding, mutagenesis

[20] http://www.macroprograma1.cnptia.Embrapa.br/gestaomacrograma1.

[21] The National Centre for Genetic Resources (CENARGEN) was established in 1974 by Embrapa following a call by the FAO for the creation of a worldwide network of Centres for Conservation of Genetic Resources in areas considered of high genetic variability. An outline of current research projects is provided on the CENARGEN website: http://www.cenargen.embrapa.br/.

[22] Two Federal institutions share responsibility for the safety assessments and final approval of new products of biotechnology: the Canadian Food Inspection Agency (CFIA) and Health Canada. CFIA is responsible, under the authority of the *Seeds Act and Regulations* (Government of Canada, 2012a), for the regulation of agricultural products derived through biotechnology, including plants, animal feeds, fertilisers, and veterinary biologics. The Agency also authorises and oversees import permits, confined trials, unconfined release and variety registration (www.inspection.gc.ca). Health Canada (www.hc-sc.gc.ca) is the federal department responsible for the assessment for human health of each new product before it can be sold in Canada, under the Food and Drugs Act (Government of Canada, 2012a). Further detailed information on the whole regulatory system in Canada for GM crops is provided by Smyth and McHughen (2008). Approval harmonisation between the Canadian and American assessment processes has also played a role in the appearance in Canadian markets of GM squash and GM papaya, where impact studies guiding the approvals were conducted in the USA rather than in Canada.

or GM technology[23]. This approach acknowledges the fact that it is the product, and not the process, that warrants regulation because it is the presence of novel traits in a plant that potentially pose an environmental or health risk, and not how the traits were specifically introduced. Regulations for biotechnology-derived crops should therefore be focused on those that possess traits sufficiently different from the same or similar species as to require an assessment of risk.

A PNT is defined as a new variety of a species that has one or more traits that are novel to that species in Canada or outside the trait range of plants currently cultivated. A trait is considered to be novel when it has both of these characteristics: (1) it is new to stable, cultivated populations of the plant species in Canada, and (2) it has the potential to have an environmental effect (Canadian Food Inspection Agency, 2012). Guidance is also provided for the stacking of traits and for re-transformation/re-mutation of PNTs. The Canadian Food Inspection Agency (CFIA) requires notification of all stacked products before they are introduced into the marketplace (Canadian Food Inspection Agency, 2012).

The environmental safety assessment of a PNT examines five broad categories of possible impacts (Canadian Food Inspection Agency, 2012), as follows:

1. The potential of the plant to become a weed or to be invasive of natural habitats.
2. The potential for gene flow to wild relatives.
3. The potential for a plant to increase the activity of a plant pest.
4. The potential impact of a plant or its gene products on non-target species.
5. The potential impact on biodiversity.

Three breeding objectives always require notification to the CFIA under the authority of the Seeds Regulations:

1. Any introduction of a new trait that significantly and negatively alters the sustainable management of the crop, for example herbicide tolerance and insect resistance (where stewardship is important to delay the development of resistant/tolerant weeds or resistant insect populations, respectively).
2. Any change to the plant which results in a novel production or accumulation of molecules that may have a harmful effect on living systems.
3. Any introduction of a new trait that may result in an increase in overall plant fitness or competitiveness in a crop for which Canada is a centre of diversity.

The development of the Canadian regulatory system since the late 1980s broadly followed several guiding principles (Thomas and Yarrow, 2012). The first principle was avoidance of unnecessary duplication in regulations and in the responsibilities using existing legislation and regulatory institutions. The development of the regulatory system also worked to increase the predictability of the regulatory trigger and capture only those plants with the greatest potential to have a negative impact on the environment. This aims to reduce the impact of these regulations on the development of innovation and on the competitiveness of Canadian plant breeders. Following a series of consultations with stakeholders, the CFIA published a directive (CFIA, 2009) intended to assist breeders, developers and importers of new plant lines in determining whether their plant requires regulation before its environmental release. In addition to this guidance, the CFIA and Health Canada offer pre-submission consultations to developers of PNTs, novel feeds and novel foods.

A further guiding principle was to increase regulatory transparency; among the key actions was the creation of the Canadian Biotechnology Advisory Committee, an expert committee to provide advice to the government on emerging issues, and to facilitate the incorporation of public input into the strategy. Canada has committed to make information available on the Biosafety Clearing-House, an international mechanism to exchange information about the movement of living modified organisms, established under the Cartagena Protocol on Biosafety. To meet this commitment, knowledge of all of the living modified organisms cultivated in Canada, regardless of whether they are PNTs, will be required.

A key strength of the Canadian regulatory system is that while the techniques used by plant breeders continue to evolve, the regulatory trigger for PNTs will remain current and consistent. In contrast, process-based approaches used in other jurisdictions (including the EU) will be challenged or become obsolete (Lusser et al., 2012a, Podevin et al., 2012; Thomas and Yarrow, 2012; Waltz, 2012). A further implication of this approach is that not all crops developed by GM technology (or any plant technology) will necessarily meet the definition of a PNT (for example, a variety carrying a gene conferring resistance to a particular disease where this trait was well established in the crop but a specific gene might be incorporated in a

[23] A list of approved PNTs, derived both by GM and by conventional technologies, is available on the website of the Canadian Food Inspection Agency: www.inspection.gc.ca.

new variety by either conventional hybridisation or genetic transformation). However, all the GM crops commercially grown in Canada so far (including crops with stacked events) have been submitted for and have received regulatory approval according to published standards.

Notwithstanding the potential strengths of the Canadian system in supporting innovation, concerns have been raised regarding several issues, including the following: the 'freedom to operate' problem that exists in agricultural biotechnology when rival firms create economic barriers for the commercialisation of second-generation GM crops; the requirement for separate approval for plants with stacked traits, pricing of new seed varieties in a concentrated sector; the rules of using new technology; and the appropriate role of the public sector, where there is evidence of a deterrent effect of the regulations (Malla et al., 2003; Malla and Gray, 2005; Galushko et al., 2010; Smyth and Gray, 2011; Brewin and Malla, 2013). Among public scientists and plant breeders there is also some frustration with the system because, in practice, it broadens the definition of what is regulated to include materials produced by technologies that are not considered elsewhere to be the subject of special scrutiny (for example plants produced from interspecific crosses).

2.4 Cross-cutting issues from international comparisons

The international experience of GM crops in these comparator countries is diverse (see also Appendix 3) and the present chapter has focused on selected facets to exemplify key points. Some general conclusions can be drawn from the evidence available.

- In most of the competitor countries surveyed, the export of agricultural commodities is an increasingly important part of their economy. This is not so in the EU, and one result of this lack of priority in the EU has been little incentive to exploit science and technology for agricultural innovation. One further consequence of this disparity is that some of the relevant areas of basic science, as well as their translation to applications, are progressing more rapidly outside the EU.

- When considering attribution of impact, it is vitally important to distinguish between any specific effect of a technology and the consequences of other changes in agronomic practice or social development. There is an increasing volume of evidence to document a range of benefits accruing from the first generation of GM crops. At the same time, the conclusion emerging from the aggregate evidence collected in the comparator countries is that GM technology has no greater adverse impact than any other technology used in plant breeding (see also Chapter 4).

- Considerable regulatory experience has been gained in countries outside the EU and it is now clear that streamlined, transparent, effective regulatory frameworks can be devised that also encourage investment. For example, Canada has a trait-based regulatory framework by comparison with the technology-focused framework in the EU. Although there is a necessary degree of pragmatism involved in judging 'what works' in regulation, it is essential that any regulatory system is evidence-based.

- Different countries use their national academies of science to varying extents to inform decision-making (see also Chapter 3). All academies of science should seek to develop effective advisory roles – and share good practice – based on the scientific evidence available. At a global level, the InterAcademy Panel provides a valuable mechanism for exploring how this might be developed and coordinated for international consistency.

These conclusions help to provide the context in which to discuss further the challenges and opportunities for the EU (Chapters 4 and 5).

3 The connections between the EU and Africa

Summary of emerging points in Chapter 3

- Evidence indicates that EU policy, practices and perspectives have sometimes constrained the use of crop genetic improvement technologies in African countries, creating difficulties for scientists, farmers and policy-makers.
- The situation across Africa is diverse but there is increasing activity to characterise and cultivate GM crops that help to address local needs in tackling biotic and abiotic stress as well as provide nutrient fortification.
- Academies in Africa have important roles in identifying science and technology priorities, strengthening centres of excellence, and contributing science-based advice to support policy-making and public debate.
- There are significant opportunities for information-sharing and R&D partnership between Africa and the EU, informed by local priorities and acting to strengthen local systems in Africa. There is also a continuing role for academies in the EU and Africa to work together in analysing and addressing science and policy issues for agricultural innovation.

3.1 Prospects for agricultural biotechnology in Africa

Agriculture accounts for about two-thirds of full-time employment in Africa and more than half of export earnings. Contrary to what is often surmised to be its traditional image, much of African agriculture has been dynamic and adaptive (Government Office of Science, 2011). However, this success must be progressively amplified, because increased production still lags behind population growth, a deficit likely to be exacerbated by new pressures from changing consumption patterns, degradation of natural resources and climate change. Most (65%) of the global increase in climate-related hunger is projected to occur in Africa[24].

Academies of science worldwide have previously demonstrated their commitment to working collectively on the analysis of problems and solutions for agricultural productivity in Africa. In their comprehensive report, the InterAcademy Council (IAC, 2004) described the problems of African food security, characterised the range of farming systems and assessed the state of R&D. Among the wide-ranging opportunities identified for African countries to increase crop yield and improve nutritional value is the possibility to capitalise on and realise genetic potential: '*The full range of biotechnology components, including the appropriate use of genetically modified organisms, needs immediate attention to help improve eco-farming*'. Written a decade ago, this remains true today[25].

It is important to remember that the application of biotechnology encompasses much more than GMOs, although it is these that have often attracted disproportionate attention and controversy. GMOs are not the only or even the primary solution to current problems in Africa and, in addition to technology, it is essential to invest broadly in infrastructure, including human resources, scientific facilities and more general infrastructure for social and economic development (see also Chapter 2). Marker-assisted selection for faster and more targeted breeding and molecular diagnostics for identification and monitoring of plant diseases play an increasingly important role in Africa (Black et al., 2011), as elsewhere. Nonetheless, there are considered to be significant prospects for using GM crops for sustainable, inclusive and resilient agricultural

[24] Mapping of individual African countries for vulnerability to hunger and climate is provided by the United Nations World Food Programme analysis on http://documents.wfp.org/stellent/groups/public/documents/newsroom/wfp243427.pdf.

[25] There are many other initiatives that analyse and propose options to tackle the issues for agriculture in Africa, providing the wider context for the current academy work. These include the following:

(1) Global initiatives, for example from: FAO on a wide range of technologies in agriculture, including the use of molecular markers, genomics and genetic modification (http://www.fao.org/biotech/biotechnology-home/en); the Consultative Group on International Agricultural Research (http://www.cgiar.org); the International Food Policy Research Institute, Strategies for African Agriculture (http://www.ifpri.org/publication/strategies-and-priorities-african-agriculture); the World Bank Department of Agriculture and Rural Development (http://www.worldbank.org.agrm); the World Economic Forum on Agriculture and Food Security (http://weforum.org/issues/agriculture-and-food-security); OECD activities relating to agriculture and biosafety (http://www.oecd.org); the Global Forum on Agricultural Research (http://www.egfar.org) and capacity building projects in Africa of the International Centre for Genetic Engineering and Biotechnology (http://www.icgeb.org).

(2) Regional initiatives, for example: the Forum for Agricultural Research in Africa (http://www.fara-africa.org; the African Union's NEPAD Comprehensive Africa Agriculture Development Programme (http://www.nepad-caadp.net); and the African Technology Policy Studies Network Agricultural Innovations Program (http://www.atpsnet.org/programmes/RCB/agriculture/index.php).

(3) Major philanthropic foundations, for example the Alliance for a Green Revolution in Africa (http://www-agra-alliance.org).

(4) EU Member State advocacy initiatives, for example Agriculture for Impact, based in the UK (http://www3.imperial.ac.uk/africanagriculturaldevelopment).

development in Africa, although concerns have also been expressed about the cost of advanced biotechnologies in plant breeding (see also Brookes and Barfoot, 2013 for analysis of relative costs). There are applications that would facilitate better use of marginal land, provide better tolerance to biotic (Gressel et al., 2004) and abiotic stresses such as drought or flooding associated with erratic weather patterns[26], as well as improve micronutrient content of staple crops (see later in this chapter and Appendix 4). Notable recent examples include improved pest and disease resistance in African crops such as cowpea (Huesing et al., 2011), rice (Verdier et al., 2011) and cassava (POST, 2012) and the initiative to deliver multiple nutrients in a single staple species, supported by the Grand Challenges in Global Health Programme[27].

A report from the Academy of Science of South Africa (ASSAf, 2010, in collaboration with the Union of German Academies of Sciences and Humanities, NASAC and the Uganda National Academy of Science) emphasised that GM crops could be a vital tool for tackling the chronic food shortages in sub-Saharan Africa. However, this conclusion was predicated on development being carried out within a framework of appropriate policy with sufficient financing for human capital development, laboratory infrastructure and the use of rigorously planned, results-oriented research.

Four countries (South Africa, Egypt, Sudan and Burkina Faso) currently grow GM crops commercially although field trials are underway elsewhere, for example in Uganda and Nigeria. In addition, Mali, Kenya and Ghana recently enacted biosafety laws to regulate applications (Okeno et al., 2013). A publication from the World Bank (McLean et al., 2012) describes how the ratification of the Cartagena Protocol has impacted on safety regulation in Africa. According to this analysis, there are new opportunities: to make sure that biosafety regulation is defined by development priorities for food security as well as by environmental protection goals; to focus on assessing plausible environmental impacts, positive and negative; to harmonise current data requirements and regulatory processes between countries; and to build capacity to strengthen the science and knowledge base.

3.2 Historical influences: the view from outside Africa

GMOs have had rather a troubled history in Africa, some of which can be attributed to the influence of the EU. Ten years ago, concern was expressed (Nuffield Council on Bioethics, 2003) that EU sources, including consumer organisations, had put pressure on developing countries not to develop GM crops. Exaggeration of the risks by European sceptics created difficulties for policy-makers in Africa: '*The freedom of choice of farmers in developing countries is being severely challenged by the agricultural policy of the European Union. Developing countries might well be reluctant to approve GM crop varieties because of fears of jeopardising their current and future export markets. They may also not be able to provide the necessary infrastructure to enable compliance with EU requirements for traceability and labelling … We conclude that the current provisions … have not taken sufficiently into account the negative effect that these policy instruments are likely to have on those working in the agricultural sector in developing countries*' (Nuffield Council on Bioethics, 2003).

These forebodings were prophetic and the concerns persist. EU influence on some governments in Africa to follow the highly precautionary approach in regulating GMOs has been mediated in several ways during the past decade (Paarlberg, 2010; Okeno et al., 2013). According to external commentators, influence was manifested through bilateral foreign assistance from EU Member States, multilateral technical assistance, cultural contacts and in two other ways.

1. The African concern that export of GM crops to EU markets (Africa's biggest trade partner) could be blocked by anti-GM crop sentiment within the EU (Black et al., 2011; Ammann, 2012). There is some evidence that this deterrent effect continues, for example with Egypt and South Africa stopping development of Bt potato for fear of losing European export markets (POST, 2012). However, other analyses indicate that EU consumer markets, while potentially having significant impact on a subset of countries, are not primary drivers of other African countries' decisions to avoid GM agriculture (Novy et al., 2011). A more differentiated historical explanation may be needed, for example in terms of particular colonial influences on present expectations and decisions (Novy et al., 2011); in particular, it has been observed that many francophone countries in Africa adopted laws based on the precautionary approach endorsed by the EU (Nordling, 2012).

2. Anti-GM crop activism in Africa – including the confusion of GMOs with other crop technologies – communicated through certain international NGOs with headquarters in Europe (some part-funded by

[26] This is a fast-moving area of science and technology worldwide. The first empirical quantification of innovation in adaptation-related crop biotechnology relevant to three forms of abiotic stress associated with climate change (drought, soil salinity, temperature extremes) has been made by analysing patent data (Agrawala et al., 2012). The projected impact of climate change on major crops in Africa has been assessed by systematic review and meta-analysis, indicating likely declines in yield for wheat, maize, sorghum and millet (Knox et al., 2012).

[27] Improving nutrition with new staple crops, available on http://www.grandchallenges.org/improvenutrition/Pages/default.aspx.

EU institutions) and other bodies (Paarlberg, 2010; Black et al., 2011; Novy et al., 2011; Ammann, 2012). One notable consequence of activism by international NGOs opposed to GM crops, analysed in detail (Mahsood, 2005), was the decision by the Zambian government to refuse GM food as part of food aid in 2002.

Although many such observations have been made from outside Africa, it is important to collect the evidence to test these observations. This was the purpose of the joint work with NASAC (section 3.3). There will be other consequences, intended or inadvertent, for agriculture in Africa as a result of what the EU does or does not do. For example, more efficient use of agricultural land in the EU will beneficially reduce the pressure to use land and valuable resources in Africa to meet the demands from EU countries for imports (European Observatory on Sustainable Agriculture, 2010), such that more land in Africa can then be used for local needs (particularly staple food crops rather than crops for export).

There have often been good intentions to make European research on global agricultural issues relevant to developing countries and to facilitate African access to EU R&D expertise[28]. The European Commission through the Directorate-General (DG) Research-organised Framework Programmes has often emphasised the international dimension of research. For example, in the current seventh Framework Programme work stream for Sub-Saharan Africa, within the bioeconomy remit, there is funding allocated to address food security and safety issues.

3.3 EASAC–NASAC collaboration to seek African country perspectives on the relationship with the EU

It is necessary to learn lessons from the past to optimise future agricultural policy. This necessitates sharing African country perspectives on the issues that have complicated EU–Africa relationships in agricultural biotechnology, to update analysis of the impact of EU policy and, thereby, provide evidence for informing future policy options for both Africa and the EU. The EASAC–NASAC work was designed to do this; evidence collection was initiated by soliciting written views from NASAC academy members (May–October, 2012), followed by organisation of a joint workshop in Addis Ababa, Ethiopia (November, 2012) in conjunction with the African Technology Policy Studies (ATPS) network. The following sections draw on the written responses received and contributions to the workshop (Appendix 5) from scientists in the Cameroon, Ethiopia, Ghana, Kenya, Mauritius, Morocco, Mozambique, Nigeria, South Africa, Sudan, Tanzania, Uganda and Zambia.

In seeking the views of African scientists nominated by the NASAC member academies, the following questions were posed:

1. The current situation in using biotechnology in agriculture in Africa.

   What is the situation now in your country regarding use of biotechnology/molecular biosciences in conventional/precision breeding and in GM crops? What are the current roles for the public research sector, private sector and partnerships, NGOs, extension services? What are the current regulatory procedures? Have external influences helped or hindered?

2. Looking to the future for Africa.

   What would your country like to do in addressing your agricultural priorities? What might be the roles of the public research sector, private sector and partnerships, NGOs, extension services? What are the impediments? How should the public be assured about food safety? What can the EU do now to help agricultural biotechnology develop in your country?

3.3.1 Case studies on GM crops

The NASAC–EASAC–ATPS workshop presented several country case studies of advancing agricultural biotechnology adapted to local priorities and conditions (Appendix 5). Many countries now engage in a high level of activity using molecular biological techniques; some of the opportunities for GM crop development are summarised in Table 3.1.

Although the current status of GM crops in different African countries is diverse, within the scientific community there is considerable recognition of the potential contribution that improved crops can make to societal challenges through increased yield and nutritional content, abiotic and biotic stress resistance and crop diversity. However, even where there is significant academic research expertise, there is often less public and policy-maker awareness of the opportunities. Where there is more general awareness of the subject, this is often confused by inaccurate perceptions of risk.

[28] For example, the European Research area on 'Improved coordination of agricultural research for development' (http://www.era-ard.org). The Platform for African-European Partnership on Agricultural Research for Development (PAEPARD, http://paepard.org) promotes research collaboration between a wide range of organisations with support from the European Commission. The DG DevCo Europeaid Food Security thematic programme also aims to support agricultural research and innovation in developing countries (http://ec.europa.eu/europeaid/how/finance/dci/food_en.htm).

Moreover, lack of capacity in human resources, including specific shortages of skills in molecular biosciences, infrastructure and R&D funding remain major constraints in many countries. To accelerate the momentum and extend activities to other countries, workshop participants agreed some general recommendations and identified key roles for academies of science (Table 3.2; and see Appendix 5 for more information on discussion points).

Table 3.1 Summary of GM crops in Africa, current and in prospect, from the NASAC–EASAC–ATPS workshop[29]

Crop	Pest/disease resistance and/or herbicide tolerance	Biofortification	Abiotic stress-tolerance
Cotton	×		
Cowpea	×		×
Banana/ plantain	×	×	
Coconut	×		
Cabbage	×		
Cassava	×	×	
Sweet potato	×	×	
Groundnut	×		
Sorghum	×	×	
Rice	×	×	× (salt-resistant)
Maize	×		× (water-efficient)

During the workshop, ASSAf also published its detailed recommendations to policy-makers (ASSAf, 2012; see Box 4), covering many relevant points for proportionate biosafety regulation in support of innovation.

Box 4 Summary of key messages to policy-makers from Academy of Science of South Africa on regulation of agricultural GM technology

1. Agricultural biotechnology can help to transform Africa's agriculture if governments establish and use efficient regulatory systems.
2. The regulation of agricultural biotechnology is knowledge intensive and should be based on peer-reviewed evidence obtained from hypothesis-testing.
3. African policy-makers should ensure that they procure and use robust scientific information and advice.
4. African national and regional science academies are sources of credible and independent scientific expertise and advice.
5. Policy-makers should create and use transparent and inclusive institutional mechanisms to engage the public in regulatory processes.
6. National policies and laws on agricultural biotechnology can only be successfully and effectively implemented if there is real political will and conviction.

See ASSAf (2012) for detailed analysis of the issues and recommendations for development of enabling biosafety regulations.

Table 3.2 Recommendations from NASAC-EASAC-ATPS workshop for continuing pivotal roles of academies of science in Africa relating to agricultural biotechnology

Recommendation from workshop	Key roles of academies of science
1. Capacity strengthening to harness technology	Identifying critical areas for national attention
2. Developing enabling regulatory framework and harmonising regulatory approaches	Identifying issues and options for science-based advisory processes (see also ASSAf, 2012 and Box 4)
3. Building public awareness, including farmers, and sharing lessons for good practice	Mobilising scientific community and developing stakeholder relations
4. Building research-policy interface to inform strategic discussions and translate R&D outputs into improved practice	Providing independent, credible and timely advice to policy-makers and those who influence them, to develop coherent, joined-up policy for continuity in the bioeconomy
5. Creating centres of excellence in R&D, possibly on a regional basis	Participating in developing, supporting and using centres of excellence

[29] Workshop presenters discussed examples from West Africa and Kenya and Uganda. In addition, other field trials of GM crops include the following (ASSAf, 2012; Okeno et al., 2013). Egypt: pest-resistance in maize, potato, cucumber, melon and tomato; abiotic stress-tolerance in wheat and cotton; South Africa: pest resistance in maize, potato, cotton, sugar cane; herbicide-tolerance in maize, cotton, soybean, sugar cane; and biofortification in cassava and sorghum.

3.3.2 What was the previous EU impact on agricultural biotechnology in Africa?

Bringing together information shared in the NASAC–EASAC–ATPS workshop with written responses to the questions received from the academy-nominated experts, various conclusions about previous EU/Member State influences can be drawn.

- European Commission funding and organisation of research and training workshops – for example in the laboratories of the Joint Research Centre – and support for research projects in molecular biosciences has been useful.

- International R&D partnerships are important for African countries but it is increasingly uncommon for these partners now to come from the EU, compared with North America and Asia. There may be a growing risk that EU skills attrition will magnify the difficulty of the EU competing for a place in international R&D partnerships. It is also important to understand that previous international linkages may have contributed to the brain drain of scientists from African countries and a loss of national expertise.

- In several African countries where there has been an active debate about biotechnology, European influences have not necessarily been helpful and some have hindered the introduction of GM crops. Negative political sentiment in the EU has influenced the political acceptance process in Africa (ASSAf, 2012), and this impact has been compounded by the perceived loss of trade when EU countries did not accept GM products from abroad. Even, if the EU did accept such imports, they would need to be labelled as GM whereas such labelling would not necessarily have been required for local or other international markets. This creates problems for separate handling of GM and non-GM products in African countries.

- Active involvement of some European-based or European-influenced NGOs, operating in the area of agriculture and consumer rights, often presenting an anti-GMO view, has led to public confusion and controversy at the political level.

Despite the problems, there was continuing enthusiasm by African countries to work with EU institutions and Member States in partnership to derive mutual benefit.

3.3.3 How might the EU help African countries in the future?

Various recommendations were made and there was agreement about the importance of EASAC bringing these issues to the attention of the EU policy-makers, emphasising the potential for benefit to Europe as well as Africa. Among the proposed priorities recommended for EU institutions and Member States are the following.

- Sharing expertise from lessons learnt to expand the knowledge base for innovation and use, and to monitor the impact of agricultural biotechnology.

- Sharing ways to engage with consumers and smallholder farmers, to support improved understanding of applications of biotechnology. In this regard, Europe can learn from African participatory experience in defining local needs and opportunities.

- Helping to incorporate understanding of the issues for benefit–risk assessment to progress options for creating enabling regulation for resilient agriculture. However, EU support for capacity strengthening to build critical mass for innovation must acknowledge sovereignty of African decisions for innovation, based on local needs and opportunities. The EU cannot prescribe solutions for others.

- Addressing misperceptions about GMOs by politicians and the public in the EU to avoid exporting these misperceptions to developing countries.

- Providing technical support and training in the tools of biotechnology, including tissue culture, integrated breeding, diagnostics, genomics and other 'omics' sciences, genetic engineering and stewardship of GM products. Supporting collaborative R&D projects to build the experience to address priorities within local agronomic systems. It is vital that the locus of these collaborations progressively moves from EU universities and other research laboratories to African ones.

There are also major opportunities for engagement between the academies of science in the EU and Africa. Workshop participants encouraged NASAC and EASAC to continue to work together to share good practice on what works in the science policy dialogue. European academies of science were invited to support academy colleagues in Africa in taking forward their key roles (Table 3.2), informed by African priorities and according to the fundamental principle of strengthening African systems. This might include support for an African inter-academies programme on agricultural biotechnology (ASSAf, 2012) for networking, training of scientists in the molecular biosciences, monitoring global trends, informing the public and policy-makers of advances in science and technology, and interpreting the integrity and implications of published research.

From the evidence and perspectives discussed in the workshop, it is clear that African countries are increasingly moving from an initial phase of receipt of externally provided technology to one of actively creating and using knowledge for innovation directed to local needs. Workshop participants emphasised that this transition must be accompanied by good public policy to effect equitable distribution of the benefits of agricultural innovation for economic and social well-being. There is another lesson here for EU countries; they must take care not to suffer the reverse transition, from once being at the forefront of developing genetic science and technology to ending up as a recipient of competitor countries' outputs.

4 Connecting the evidence base and EU policy development

Summary of emerging points in Chapter 4

- Evidence indicates that the slow and expensive EU GM regulatory framework has acted as an obstacle to agricultural innovation. The EU is falling behind international competitors in efficient land use for food production and other applications in the bioeconomy.
- There are important implications for the EU relating to the following: (1) critical mass and multidisciplinarity of public sector science and the provision of future skills; (2) viability of a diverse private sector, with the aim to encourage smaller companies and open innovation alongside multinational companies; (3) capitalising on research opportunities coming within range for new GM crop traits; (4) developing and using New Breeding Techniques; (5) developing new applications for the bioeconomy, for example for human health and production of green chemicals; (6) facing major environmental challenges, for example those associated with climate change and shifting pest and pathogen populations; (7) ensuring informed public engagement to support choice, political debate and priority-setting; (8) achieving strategic coherence to tackle current policy disconnects within the agriculture sector and between it and other sectors.
- There is a need to modernise and reformulate the regulatory framework for GM crops to be science-based, transparent, proportionate and predictable, taking into account the extensive experience gained worldwide.
- Academies of science in the EU have an important public role to play in reviewing the scientific evidence and clarifying what information is reliable.

4.1 Emerging conclusions on global socio-economic and environmental impacts

Chapters 2 and 3 have discussed some of the evidence available to exemplify the multiple roles and impacts of GM crops in agriculture worldwide. There are methodological issues associated with impact assessment (Chapter 2 and Appendix 4) and data quality is sometimes a limiting factor in the evaluation. Nonetheless, many scientists have concluded (for example, Qaim, 2009; Carpenter, 2010, 2011; Park et al., 2011; Lusser et al., 2012b; Mannion and Morse, 2012) that there is now a sufficiently large body of evidence on herbicide-tolerant and insect-resistant GM crops to substantiate their use in contributing to sustainable development goals.

For example, from a comprehensive review of published work it was concluded that '*available impact studies show that these crops are beneficial to farmers and consumers and produce large aggregate welfare gains*', together with environmental and health benefits (Qaim, 2009). Taken together, the published evidence indicates that, if used properly, adoption of these crops can be associated with the following:

- reduced environmental impact of herbicides and insecticides;
- no/reduced tillage production systems with concomitant reduction in soil erosion;
- economic and health benefit at the farm level, particularly to smallholder farmers in developing countries;
- reduction in greenhouse gas emissions from agricultural practices.

The issue of whether GM crop technology is a cause of environmental damage has been controversial and, of course, it is critically important that the scientific assessment of the benefit–risk balance takes account of environmental as well as human safety issues. Extensive review of the data available on crops relevant for agriculture in Europe (Sanvido et al., 2007; Sehnal and Drobnik, 2009; DG Research, 2010a; Balazs et al., 2011) provides no validated scientific evidence that the cultivation of GM crops has caused any environmental harm. A recent comprehensive assessment from the Swiss National Science Foundation (2012), reviewing more than 2000 studies, confirms that no health or environmental risks have been identified related to GM technology. A recent statement by the Board of Directors for the American Association for the Advancement of Science (AAAS, 2012) also reaffirms that GM crops are the most extensively tested crops ever added to the food supply chain, with the evidence showing that crop improvement by biotechnology is safe and that GM and their non-GM counterparts are nutritionally equivalent.

Some of the controversies in the early phase of technology development arose from uncertainties in incomplete datasets, for example relating to the putative effect of GM crops on non-target organisms and on soil ecosystems or lack of long-term experience relating to the possibility of gene flow to wild relatives or invasiveness in natural habitats (Sanvido et al., 2007). It is important for the scientific community to continue to develop evidence-based criteria for the consistent evaluation of specific effects on the environment to assist regulatory authority assessment of direct and indirect impact and to inform the public dialogue.

Assessment of broader impacts is also important (see also Appendix 4). For example, the large-scale adoption of insect-resistant Bt cotton and maize varieties has caused area-wide declines in major pests in the USA (Carriere et al., 2003; Hutchison et al., 2010) and China (Wu et al., 2008). Thus, Bt cotton paved the way for a successful eradication programme against the invasive pink bollworm, originating in Asia, thereby eliminating a problematic pest from the south-western USA (Naranjo and Ellsworth, 2010). Economic analysis revealed that the decline of the European corn borer in areas planted with GM crops has also led to significant benefits for non-Bt maize growers (Hutchison et al., 2010). In addition, evidence is beginning to emerge (Lu et al., 2012), that a beneficial consequence of applying less external pesticide to plants engineered to resist pests is the increase in natural insect predators that thrive and spread. Hence, environmental benefits are extended to neighbouring landscapes. Knock-on effects can also be measured at the macro-economic level. Spill-over of crop yield benefits and cost reductions are important globally as – through trade – they influence prices for countries importing GM crops. Models estimate that world food price increases would be higher by 10–30% in the absence of GM crop cultivation (Lusser et al., 2012b; and see Chapter 2).

4.2 Reforming EU regulatory approaches

There is abundant and accumulating evidence from extensive worldwide experience for benefit, and lack of evidence for environmental or human health risk associated with GM crop technology. Thus, there is a compelling case for the EU to re-examine its current policy governing the broad area of agricultural biotechnology. The current EU approach to regulating GM crops is hampering its potential contribution to food security and is weakening EU capacity in other ways (see Box 5). This view is shared widely across the public sector scientific community (for example, Dixelius et al., 2012)

Box 5 Is innovation in the EU falling behind?

- The current EU regulatory framework adds to the time and cost of new crop development in Europe – on average four years and €7 million direct costs per variety (Anon., 2012b).
- In 2011, the EU conducted the lowest number of field trials since 1991, when records began (Marshall, 2012; and see chapter2). The current system of GM crop field trial notification has been characterised as '*… haphazard, unbalanced and overly complex, strongly discouraging investment*' (Gomez-Galera et al., 2012).
- Field trial vandalism has also been a major problem in Europe, systematically destroying experiments by academia, industry and government research institutes (Kuntz, 2012). This extreme opposition by anti-GM crop activists has created high costs for approved field trials additional to the already substantial costs of regulatory supervision (Bernauer et al., 2011; Gomez-Galera et al., 2012)[30].
- There is a considerable backlog in pending applications on GM crops in the EU (www.transgen.de; and see Chapter 2) and lack of consistency in handling, such that some applications have been delayed for many years despite the availability of a risk assessment report.
- Only one new GM crop has been licensed for cultivation in the past 14 years. EU opportunities missed by not accepting GM crops include lost revenue for farmers and breeding companies,

Box 5 (Continued)

reduced agricultural productivity and sustainability, lost technology innovation.

- Based on modelling from case study analysis in Sweden (Fagerstrom et al., 2012), EU-wide acceptance of GM potato, oil seed rape and sugar beet would yield an economic gain to farmers of about €2 billion annually; about 645,000 hectares of agricultural land would be spared and, hence, available for other purposes. See further details on sugar beet in Box 6.
- One other consequence of the current situation is that only the largest companies in the seed business have the financial capacity to support the lengthy and costly procedures of seeking GM approval. Smaller companies are deterred as are new spin-offs from public sector plant science research (STOA, 2010).
- The discontinuation by BASF of breeding efforts for GM crops adapted to European conditions and, in particular, the loss of a *Phytophthora infestans*-resistant GM potato variety for EU agriculture (a key target for improved EU agriculture, O'Brien and Mullins, 2009), increases the likelihood of EU economic loss from potato blight, ensures reliance on continued use of fungicide and further increases the dependence on imported potatoes (Dixelius et al., 2012).
- In areas of Spain with particularly high corn-borer infestation, sustained commitment to adopting Bt-maize (Chapter 2 and Meissle et al., 2011) has led to significant economic benefit for farmers (Fundacion Antama, 2012).

[30] In Switzerland, the government finances establishment of a protected field site enabling interested research groups to conduct field experiments with GM plants (Romeis et al., 2013).

Fagerstrom et al., 2012; Giddings et al., 2012) and parliamentary committees (for example, House of Lords European Union Committee, 2010).

One recent publication (Dillen et al., 2013, co-authored by the European Commission's Joint Research Centre) on GM sugar beet, exemplifies how Europe lost its initial lead (Box 6).

If policy re-examination were to lead to more active testing and uptake of GM and other crop genetic improvement technologies, various beneficial consequences might accrue:

- helping to tackle the priorities for European sustainable food production;
- increasing EU competitiveness in global agricultural innovation;

Box 6 Case study on GM sugar beet

- In 2007, GM herbicide-tolerant sugar beet was commercialised in the USA and Canada. The speed of uptake by farmers was unprecedented, with an adoption rate of 95% within two years. Analysis suggests that adoption has been economically sound for farmers and has high potential to reduce the environmental impact of sugar beet production.
- The origins of GM sugar beet were in Europe, with field trials in the1990s. However, interest by the technology providers in the EU declined once it was decided (Regulation EC 1830/2003) that all products derived from GM ingredients should be labelled regardless of the presence of protein or DNA in the final product (sugar from sugar beet is 99.7% sucrose).
- GM sugar beet in the USA was estimated to generate US$177 million in 2010; two-thirds accruing to farmers, and one-third captured by technology providers. Total potential annual economic benefits of GM sugar beet worldwide are estimated at US$1.1 billion. It is further estimated that the EU is foregoing €300 million each year that the technology is not commercialised.
- Potential new competitive pressures on the EU sugar sector from increasing supply from least developed countries may create additional incentives for EU adoption of GM sugar beet.
- An application for cultivation of GM sugar beet was originally submitted in the EU in 2000. A decision is still pending.

Source: Dillen et al., 2013.

- lessening the potential for negative impact on those other regions that look to the EU for leadership in science and technology;
- increasing non-food biomass production;
- reducing the EU global environmental footprint associated with heavy reliance on imported agricultural products.

The need for coherent regulation of well-tested technologies grows, not just because of the societal challenges discussed previously but also because other new legislation in the EU designed to improve the environmental credentials of farming through reduced nitrate load on the land and decreased use of chemical protectants (O'Brien and Mullins, 2009) creates additional constraints for maintaining and improving agricultural productivity (see section 4.7.1).

Priorities can be defined (O'Brien and Mullins, 2009; Royal Society, 2009) for GM crop improvements most needed to tackle European challenges. These priorities appertain primarily to the major crops currently receiving high applications of pesticides or fertilisers; that is to find new ways to protect crops from pest and disease at a time of reduced chemical protection methods. Priorities include introducing insect-resistance and herbicide-tolerance into wheat, barley, oil seed rape, soybean, potato, vegetable brassicas and other horticultural crops. Other key objectives include oil seed rape with increased oil yield, wheat and maize with increased nitrogen use efficiency, cold-tolerance in maize, drought tolerance in potatoes and enhanced digestibility in forage maize and barley. Sunflower production is another example where the EU is currently not using technology to prepare for likely future constraints on yield.

The legal framework covering GM crops (Plan and Van den Eede, 2010) is currently governed by the European Commission's Directive 2001/18/EC on the deliberate release of GMOs into the environment (for cultivation) and 98/81/EC on the contained use of GMOs together with Regulation 1829/2003 in GM for food and feed. This framework embodies the precautionary principle (Sehnal and Drobnik, 2009), advising caution in adopting new technology, but unfortunately the application of this principle in practice sometimes neglects the essential condition, '*…that an adequate interpretation of the precautionary approach would require comparison of the risks of the status quo with those posed by other possible paths of action*' (Nuffield Council on Bioethics, 2003).

Even if stringent application of the precautionary principle had been justifiable in the early days of GM crop R&D when there were more uncertainties about impact, it is difficult to defend the merits of retaining a rigid, cautious, technology-specific regulation today when there is much less uncertainty. There is urgent need to recalibrate the

level of scrutiny applied to this and other crop genetic improvement technologies, to ensure that EU regulatory assessment is not disproportionate, has a sound basis in evidence and experience (Fagerstrom et al., 2012; Giddings et al., 2012), and is applied in a manner that is consistent with other regulation, within and outside the sector. For example, if new understanding on criteria for determining ecological harm was incorporated consistently in formulating regulatory decisions governing all agricultural management practices it would help to improve strategic coherence (Sanvido et al., 2012), particularly if coupled with streamlining of assessment.

The mission of EASAC embodies the core principle that an appreciation of the scientific dimension is a prerequisite to wise policy-making. We emphasise that, as well as informing new policy, the canonical scientific evidence must be used as a tool rigorously to test and audit current policies, to assess 'what works'. From our perspective, assessing the deliverables from agricultural biotechnology and applying international benchmarks, EU policy is definitely not working.

It is not our present purpose to describe in detail the current difficulties associated with seeking EU approval for GM crops, because these points are well-described in the literature cited previously. External evaluation of the advisory body, the European Food Safety Authority (EFSA) has confirmed that its performance is high quality, professional and independent (Ernst and Young, 2012). Recently, EFSA has announced a major initiative to facilitate access to data for enhancing transparency in risk assessment and is now considering how best the technical data used in risk assessment can be made available to the broader scientific community and interested parties (EFSA, 2013; Butler, 2013).

However, the current regulatory approval system is expensive, time-consuming and inappropriately focused on the technology rather than the product. There is an increasing complexity of authorisation requirements arising from the progressive introduction of new requests for risk assessment and management that may not have a scientific basis, and there is need to streamline procedures. There is also inconsistent and inefficient linkage between the recommendations of the EFSA and political action for final expeditious approval. In particular, some Member State politicians ignore the decisions of the advisory committees and the European Commission (Fagerstrom et al., 2012), despite the repeated confirmation of a core tenet (EGE, 2008), '*… food safety standards have to be based on scientific data only*'.

In addition to political pressures pre-approval, extra delay post-authorisation is incurred when Member States invoke the safeguard clause of Directive 2001/18/EC. This clause provides that where a Member State has justifiable reason to consider that a GMO, which has received consent for placing on the market, constitutes a risk to human health or the environment, it may provisionally restrict or prohibit use or sale of that product on its territory. In 2013, Poland joined seven other Member States that had introduced safeguard bans on cultivation of GM-crops. However, in all cases where the safeguard clause was invoked, the European Commission deemed that there was no new evidence which would justify overturning the original authorisation decision[31]. The European Court of Justice has recently clarified the legal requirement for the cultivation of GM crops in Member States. It confirms that additional national authorisation procedures introduced on top of the existing approval process conducted by the EFSA are unlawful (European Court of Justice, 2012).

On the basis of its evaluation of the GMO legislation, the European Commission acknowledges that adjustments are necessary to make the authorisation system more efficient (DG Sanco, 2011). EASAC suggests that more radical reform of GMO legislation is warranted, so as to be consistent with other international regulatory approaches and to learn from what has succeeded in regulation of innovation in other sectors. This mandates redirection of focus from technology to product regulation as a goal and to benefit–risk rather than risk alone. This is a theme that EASAC has developed in our broader analysis of innovation across the sectors (EASAC, 2010; EASAC-JRC, 2011). The healthcare sector is now evaluating ways to evaluate benefit–risk, to take account of user priorities (FDA, 2012) and, by analogy, regulation of agricultural innovation should take better account of societal priorities (Butschi et al., 2009; Potrykus, 2012). In the short-term, it is suggested that it would be desirable to introduce regulation on the basis of the conferred trait rather than the technology deployed to deliver the trait (see Chapter 2 for examples of international good practice). Trait-based regulation would facilitate the simpler approval of novel crops closely related to those already approved and, in consequence, would be expected to encourage innovation by smaller companies as well as boosting GM plant diversity.

4.3 Impact on the science base

The slow and unpredictable pace of GM crop regulatory approval and commercialisation is harming R&D. Private sector research resources are being lost from the EU (Dixelius et al., 2012). There has also been progressive reduction in the public sector science base (STOA, 2010), which – despite the strong history of plant sciences and

[31] DG Sanco, 'GMOs in a nutshell', available on http://ec.europa.eu/food/food/biotechnology/qandq/d1_en.htm. This is illustrated recently in the EFSA Scientific Opinion on GM oil seed (EFSA Panel on Genetically Modified Organisms, 2012).

biotechnology in academia in Europe (Royal Society 2009; Sehnal and Drobnik, 2009; Balazs et al., 2011) – is weakening the capacity of the EU to develop solutions for its specific agricultural needs and to contribute to tackling the global challenges (EPSO, 2011, 2012). Major agricultural research institutes have closed (House of Lords European Union Committee, 2010) and the sector is facing fragmentation and continuing reduction of funding. In consequence, as noted in the statement from the German academies of science (German National Academy of Sciences Leopoldina et al., 2009), '*We are in the process of exporting excellently qualified researchers instead of highly advanced seed and agricultural technologies*'. There is now a shortage of relevant skills required for the bioeconomy (European Commission, 2012b). Attending to the problems described earlier in this chapter, can be expected to lead to decreased permanent loss of scientists to countries outside of the EU, increased employment in science in the EU and increased gross domestic product.

The expanding frontier of crop genetic improvement technologies necessitates a cross-disciplinary scientific approach. Some key areas of science are dangerously vulnerable to attrition as a consequence of the specific difficulties facing agricultural biotechnology in the EU together with a more general impact of the CAP that had assumed that food security in the EU was no longer a problem. These areas of science include the following: botany, plant breeding, soil science, pathology, crop physiology, entomology, weed biology and environmental microbiology (Royal Society, 2009). It is vital that research funding bodies at the Member State and EU levels address the skill gaps but the revival of these subjects should not be at the expense of effort in molecular biology and genomics, which continue to be fundamental to all aspects of genetic improvement (Royal Society, 2009). There is a further problem. A loss of skills to translate basic molecular biology advances into practical outcomes has meant that research outputs have not been taken forward within the EU but rather that the benefit of their application has accrued in other countries. In addition, it is necessary to revitalise public sector plant breeding efforts and rebuild the linkage with academic research outputs.

EASAC shares the concerns that the competitiveness of the science base is weakening in this sector, although we emphasise that excellent science can still be found in many Member States. What is needed is the rebuilding of critical mass. The European Commission's launch of the new ERA-NET, for coordinating action in plant sciences (www.eracaps.org) is welcome in attempting to support collaborative projects and share outputs. Nonetheless, the European Commission and Member States must, additionally, invest in more research capacity and for the long-term, as well as devise the supportive regulatory framework to enable research outputs to be rapidly translated into innovation as discussed in the preceding sections. At the same time, it is important to integrate advances in the natural sciences with the social sciences, so that new ideas and technologies can be disseminated effectively throughout society (Anon., 2012a).

4.4 Impact on new technology development

As observed previously, a new set of tools is in prospect as a consequence of advances in biotechnology (Chapter 1, Box 3). These advances in New Breeding Techniques within the broad array of crop genetic improvement technologies bring within range additional ways to endow plants with the desired traits more precisely and efficiently. However, at the EU level, there is currently some confusion as to how these New Breeding Techniques should be regulated. Until legal clarity is reached, application is hampered (Tait and Barker, 2011). The registration costs are likely to be low if a technique (and its products) is classified as non-GMO but very high if classified as GMO and, therefore, subject to the same regulation as transgenic approaches. This distinction will, again, be of particular importance for small-medium sized enterprises and public sector researchers seeking to commercialise their outputs; classification as a GMO would limit application exclusively to traits for high-value crops.

The European Commission's DG Environment has taken an important initiative in assembling a group of experts from the national regulatory agencies to evaluate whether certain New Breeding Techniques constitute genetic modification and, if so, whether the resulting organism falls within the scope of GMO legislation (Lusser et al., 2010). The recent advice from this New Techniques Working Group (Podevin et al., 2012) is most helpful in providing evidence-based perspectives on each of the novel approaches, clarifying and documenting where new breeding techniques fall outside the scope of current GMO legislation. Their findings are compatible with the emerging consensus in the scientific literature (Waltz, 2012), which is beginning to bring about change in regulatory thinking in the USA. In the first of the safety assessments – on cisgenesis – commissioned from EFSA on the New Breeding Techniques, the EFSA expert panel concluded that the hazards were similar for cisgenic and conventionally bred plants (EFSA, 2012b); it is also notable that cisgenesis attracts more public support than transgenesis (see section 4.5). A second safety assessment (EFSA, 2012c), noted that use of the zinc finger nuclease and other site-directed nucleases can minimise hazards associated with the disruption of genes or regulatory elements in the recipient genome.

These scientific findings have important implications for the application of regulatory principles and it is vital that the EU legislative position is fully informed by the advancing scientific evidence. It is also vital that the processes for deciding on regulatory oversight are transparent and that the new evidence base used for

decision-making is accessible by the wider scientific community. These matters are important (Podevin et al., 2012) and EASAC is concerned that many European policy-makers, by contrast with policy-makers elsewhere, may not yet appreciate the significance for food security of the new techniques emerging (Atanassov et al., 2010). Notwithstanding the general importance of recalibrating GMO legislation, discussed earlier in this chapter, as a short-term consideration it is also important for EU regulators to confirm that the products of the New Breeding Techniques, when they do not contain foreign DNA, do not fall within the scope of GMO legislation. This clarification of status would give strong, immediate support to the competitiveness of the EU plant breeding sector which, thus far, has been responsible for a significant proportion of the worldwide research on New Breeding Techniques.

Much innovative thinking and experimentation has gone into the development of new technologies for crop genetic improvement. Patented intellectual property attaches to some of the New Breeding Techniques but terms of license may still stimulate innovation among public sector researchers and smaller companies. It would be perverse if the costs of regulation in the EU were again to provide an impediment such that the 'cost of entry' could only be afforded by large multinational companies interested in markets for globally traded crops.

4.5 Public attitudes and engagement

Discussion about GM crops tends to have become a proxy for other much-needed discussion about food shortages and price increases, food safety and farming systems, as well as about social justice, international trade agreements, fair competition, economic power of multi-national companies and the apparent conflict between intellectual property protection and benefit sharing (Royal Society, 2009; Sense about Science, 2009). These broad controversies cannot be settled by focusing debate onto a single technology.

Survey data indicate that public respondents across the EU often express negative sentiments about GM food (DG Research, 2010b). To some extent, the response is influenced by the framing of the question; for example, 'transgenic' is sometimes deemed safer than 'GM'. In all EU countries the new breeding technique of cisgenesis receives higher public support than transgenesis (DG Research, 2010b; Podevin et al., 2012). Moreover, as indicated in the response to the CAP consultation, there is a high level of public agreement that farmers should be encouraged to take advantage of biotechnology (European Commission, 2010). This support was confirmed in analysis of the more recent responses to the consultation on the potential of the bioeconomy to address key challenges in Europe (European Commission, 2012b); the greatest expression of public confidence was for a role of the bioeconomy in securing a sufficient supply of food and biomass. It was noteworthy that NGOs expressed much greater concern on potential risks than did the public.

There is also a growing body of evidence to show that the actual GM food purchase behaviour of consumers does not correspond to their stated, sceptical attitude, '*… when GM food products are available on the shelves, consumers are generally willing to buy them*' (conclusion reached from EU Framework Programme 'ConsumerChoice', discussed in JRC–FAO workshop, Lusser et al., 2012b). Accordingly, as highlighted by DG Environment (DG Environment, 2012), previous surveys may have exaggerated the extent of negative feeling towards GM products and it may be that GM foods will become increasingly acceptable, if the advantages (such as lowered pesticide residues and competitive price) are clearly indicated.

Emerging evidence also indicates that European farmers are willing to adopt GM crops (Areal et al., 2011). To a significant extent, farmers share the attitudes of public sector scientists in calling for streamlining of the GM regulatory framework and for better engagement between the farming, scientific and policy-making communities and the public (Farmer Scientist Network, 2012).

Public participation in discussions about agricultural innovation remains highly important (EGE, 2008; Butschi et al., 2009) and further work is required to optimise the methods for engagement (including use of the social media, Rutsaert et al., 2012). The European Commission has funded useful research on communication (DG Research, 2010a) and excellent public information is available from other sources (for example, Sense about Science, 2009). The scientific community needs to maintain its commitment to engage with the public about the value of new techniques, and scientists have a responsibility to communicate proactively in ways that are understandable to society at large. Academies of science have an important role to play in reviewing the evidence and providing clarity about reliable information. As part of this commitment, EASAC will produce a lay summary of the present report and will stimulate continuing discussion with citizens in the Member States. However, EASAC also emphasises that responsible policy-making requires leadership founded on carefully weighing all the evidence and not just following public opinion.

4.6 Intellectual property

There is no doubt that patenting in biotechnology has raised strong emotions. The issues have been broadened by bringing in various public interests through the Convention on Biodiversity and private interests through

the World Trade Organization Agreement on Trade-Related Intellectual Property Rights (Black et al., 2011).

Quite a lot has happened since the discussion in the InterAcademy Council report (2004) about the opportunities for developing countries to appropriate the benefits of agricultural biotechnology. At that time, there were few good examples of technology-sharing and benefit-sharing schemes, but the need to share was emphasised (IAC, 2004). Although the first generation of GM products were clearly the private intellectual property of multi-national companies, more recently, GM crop development in Africa and elsewhere has often been publicly funded with support from international foundations and agencies (Anon., 2010; Black et al., 2011; Ammann, 2012; Grushkin, 2012; and see Chapters 2 and 3).

In consequence, there is increasing experience with models to support the sharing of intellectual property or the free licensing of outputs for public use (some examples are shown in Table 4.1), within the broad context of efforts to balance the objectives for wider dissemination of research outputs and tools with protection to encourage private investment and commercialisation (CGIAR, 2012).

Other examples of collaborative activity in open innovation were described in the EASAC report on synthetic biology (EASAC, 2010) and may serve as additional models to extend to agricultural biotechnology. One key issue for any approach to benefit sharing is to consider how a proportion of the benefits can be returned for reinvestment into publicly funded research (POST, 2012).

In addition, examination of the options for protecting intellectual property rights in agriculture must also take into account the issues for maintaining co-existence between breeder's rights and patents (Jacobsen et al., 2011). The intergovernmental convention of the International Union for the Protection of New Varieties of Plants (http://www.upov.int) encourages plant breeding by granting breeders of new varieties an intellectual property right for the benefit of society – the breeder's right. However, this system is under pressure from the increasing patenting of plant traits, a monopoly right. The benefits of plant variety protection have been described in detail elsewhere (UPOV, 2005) and it is important to ensure an internationally harmonised regulatory environment for intellectual property, with support for stimulating open innovation, that enables farmer access to high-quality seed at a fair price (FAO, 2008) and sustains the viability of the breeding company sector (European Seed Association, 2012). In this context, it is highly relevant that the scope of a forthcoming European Commission expert report[32] on the development and implications of intellectual property law in the field of

Table 4.1 New approaches to collaborative activity and open innovation in agricultural biotechnology

Initiative	Scope	Reference
Public Intellectual Property Resource for Agriculture	Creating patent pools to develop open-access technologies; consolidating patent property rights for both commercial and non-commercial applications.	Chi-Ham et al., 2012, http://www.pipra.org
African Agricultural Technology Foundation	Acting as broker to facilitate the transfer of royalty-free biotechnology for research to benefit African smallholders.	http://www.aatf-africa.org
Golden Rice project	Biofortified (beta-carotene) rice distributed to developing country farmers free of royalties. Public–private partnership was very helpful in achieving free licensing of the technology while ensuring product development.	Potrykus, 2010, http://goldenrice.org
Pharma-Planta Framework Programme Project	EU-funded consortium has agreed to humanitarian use statement that guarantees project technology will be transferred to developing country settings and intellectual property will be donated.	http://ec.europa.eu/research/health/infectious-diseases/poverty-diseases/projects/93_en.htm
CAMBIA-BIOS	BIOS is the agricultural biotechnology application of CAMBIA, open source initiative to share new (patented and non-patented) technologies and tools.	http://cambia.org, http://www.bios.net
2 Blades Foundation	US-based foundation, seeking to improve crop disease resistance, leases its intellectual property free to philanthropic concerns while money from commercial applications is invested back into research.	POST, 2011, http://2blades.org

[32] 'Biotechnological Inventions' initiative announced December 2012, http://ec.europa.eu/internal_market/indprop/invent/index_en.htm.

biotechnology will cover both patent law and the law on plant variety rights.

4.7 Looking forward: new challenges, new products, new strategies

4.7.1 Shifting pathogen populations and other environmental changes

Pathogen populations

Wheat, barley and potato are primary tillage crops across Europe but all three succumb to significant disease pressures that growers have to counter with the use of high inputs of fungicides. Unsustainable in the long-term, the current strategies have led to an accelerated rate of genetic change in pathogen populations. For example, *Septoria tritici* blotch disease is the primary pathogen of European wheat necessitating about 70% of Europe's annual cereal fungicide use to mitigate yield losses. Yet, the evolution of fungicide resistance in populations of *Septoria tritici* blotch (Fraaije et al., 2007; Cools and Hammond-Kosack, 2013) has led to the elimination of strobilurins and several triazole classes as effective agents of control. Similarly, the emergence of novel strains of potato late blight disease (*Phytophthora infestans*) has created significant challenges to potato production (Cooke et al., 2012). New approaches to generating durable biotic resistance in crops are needed urgently.

Climate change

The previous EASAC report on *Plant genetic resources for food and agriculture* (EASAC, 2011) discussed the increasing policy challenges in the EU associated with CAP reform in general and food security in particular, with concomitant objectives for promoting sustainable rural development and avoiding continuing loss of biodiversity. That report also noted the impending likely problems for agriculture attributable to climate change and welcomed the proposed strategy (European Commission, 2009) for combining action to make better use of existing genetic diversity and capitalising on new opportunities offered by biotechnology. The European Commission's highly important Joint Programming Initiative on Agriculture, Food Security and Climate Change is now underway (European Commission, 2011c). The application of plant sciences should have a central role in this initiative (EPSO, 2012) in delivering the stated objectives for sustainable intensification of agricultural systems, balanced with biodiversity and ecosystem services, and accompanied by greenhouse gas mitigation. Although we cannot be certain how climate change will affect agriculture in Europe (EASAC, 2011), we do know that improved crop traits will be required to adapt to more variable local conditions. It is likely that northern Europe will experience a warmer and more humid climate subjecting crop productivity to increased biotic stress from insects, and fungal pathogens, whereas crops in southern Europe will have to be adapted to drier conditions (O'Brien and Mullins, 2009; Fagerstrom et al., 2012).

To reiterate a previous point, these challenges will be compounded by the impact of EU environmental legislation governing use of water (Water Framework Directive 2000/60/EC), nitrates (Directive 91/676/EEC), phosphorus (Dangerous Substances Directive 76/464/EEC) and pesticides (revision of Pesticide Directive 91/414/EEC), creating new opportunities for GM crops to contribute to agricultural policy objectives (O'Brien and Mullins, 2009; Tardieu and Hammer, 2012).

In addition to these domestic objectives, it is also highly desirable for EU R&D to play its part in tackling the wider global challenges to agriculture arising from climate change. There is much research to be done to assess how these challenges will affect yield. Investment in research, for example *in silico* modelling and systems biology analysis, is needed now to identify the likely physiological traits required, followed by testing in controlled environments modelling likely future scenarios.

4.7.2 The food crop pipeline

The current major GM crops commercialised worldwide involve relatively simple changes to provide herbicide tolerance and insect resistance. In addition to the progressive combination of existing traits (stacking of individual GM events), the next decade will see a broader market introduction of new agronomic traits such as drought resistance, virus resistance, nutritional improvements (beta-carotene in rice and altered fatty acid profile in soybean) and the extension of modifications to other crops (Stein and Rodriquez-Cerezo, 2009, 2010). It has been predicted that technology providers will increasingly emerge from Asia as a major source of GM events (Stein and Rodriguez-Cerezo, 2009, 2010; Grushkin, 2012). For example, the Chinese government policy statement in 2010 committed to the industrialisation of GM food crops following on from major investment in plant sciences in rice, maize (for better use of phosphorus in animal feed), rapeseed, soybean, sweet pepper, papaya, and wheat, variously for yield, quality, nutritional value, drought tolerance, salinity tolerance and pest-resistance. Recent evidence collated by FAO indicates a considerable quantity and variety of GM crops in the pipeline that may be commercialised in developing countries within the next 5 years (Ruane, 2013; see Chapter 2).

As discussed previously, there will be continuing progress in combining genetic modification technology with improved plant breeding to accelerate trait selection (Royal Society, 2009; Grushkin, 2012) and the impact of the New Breeding Techniques will become increasingly apparent (Lusser et al., 2012a, b; Grushkin, 2012). It can also be predicted (see Chapter 2) that if disparities in the approval rate of GM events worldwide (asynchronous approval)

persist then the current complications in international trade will be exacerbated, to the detriment of EU food and feed security in the short-medium term (Butschi et al., 2009; Stein and Rodriguez-Cerezo, 2009, 2010).

Further ahead, scientific discovery worldwide may enable much more radical options for GM crops, involving highly polygenic traits (Royal Society, 2009; Godfray et al., 2010; Grushkin, 2012; Bennett and Jennings, 2013). Next generation DNA sequencing (Edwards et al., 2012) and advances in high-throughput genome assembly and analysis are aiding understanding of the most complex plant genomes (Morrell et al., 2012). Transcriptomics (Jiao et al., 2009), proteomics and metabolomics (Fernie and Schauer, 2009) are providing new insights into plant cell function and development. Many more genes are now available with which to engineer traits and it is increasingly possible to refine control of the introduced gene to render its effect more precise and efficient.

Among the longer-term targets now coming within range are the following:

- Further improvement in resistance to fungal, bacterial and viral infections, tolerance to drought, soil salinity, higher temperature.
- Staple cereal crops that are perennial rather than annual, reducing need for tillage and, hence, lessening soil erosion.
- Reduction of losses before harvesting by influencing traits, such as reduced shattering in cereal and oil seed crops.
- Cereals that can fix nitrogen in the same way as legumes, sparing the use of nitrate fertilisers.
- Increasing efficiency of solar energy use and storage through photosynthesis. For example: replacing the normal C3 photosynthesis in rice by C4 (von Caemmerer et al., 2012), which is more productive at higher temperatures; capitalising on better understanding of the photosynthetic systems from bacteria or algae; and maximising photosynthesis by altering crop architecture, leaf area and leaf angle.
- Increasing yield in other ways, for example by taking account of the new scientific understanding of the circadian rhythm that determines flowering, and of root structure to increase crop density and improved mineral nutrition.
- Progress on other approaches to nutritional changes, for example improving amino acid balance in cereals, modifying wheat protein to allow consumption by those with celiac disease, modifying other proteins to reduce allergy, and decreasing crop toxin levels (both exogenous mycotoxins and endogenous cyanogenic glycosides).

4.7.3 New applications for the bioeconomy

Agricultural biotechnology has potential to contribute to societal objectives in pursuit of the bioeconomy in other ways (Butschi et al., 2009; European Commission, 2012a). There is considerable R&D activity, including in the EU, underpinning the search for next generation bio-energy (DG Research, 2010a; Grushkin, 2012). As this topic has been addressed in detail recently by both the German National Academy of Sciences Leopoldina (2012) and by EASAC (2012), it will not be discussed any further here. Additional applications within the bioeconomy include horticulture, forestry, the generation of plant-based pharmaceuticals and other chemicals, as building blocks for industrial synthesis. After a slow beginning, the production of proteins for application in human health is now making progress (Table 4.2).

The USA is leading in many of these healthcare applications although the HIV-neutralising antibody

Table 4.2 GM plant protein applications in human health

Therapeutic/ prophylactic Class	Candidate recombinant protein	Plant system	Status
Enzyme replacement therapy	Glucocerebrosidase (taliglucerase alfa) for type I Gaucher's disease	Suspension cultured carrot cells	First FDA-approved biological drug for human use, manufactured in plant cells
Hormone therapy	Insulin for diabetes	Safflower	Phase II clinical trial
Cytokine therapy	Interferon alpha for hepatitis C	Duckweed	Phase II clinical trial
Transferrin therapy	Lactoferrin (VEN 1000) for antibiotic-associated diarrhoea	Rice	Phase II clinical trial
Monoclonal antibody	Neutralising *Streptococcus mutans* (Caro Rx) for dental caries	Tobacco	Phase II clinical trial
Monoclonal antibody	Neutralising HIV (P2G12) for HIV infection	Tobacco	Phase II clinical trial
Vaccine	For H5N1 influenza	Tobacco	Phase II clinical trial

Sources: DG Research, 2010a; Grushkin, 2012; Maxmen, 2012; Wilson and Roberts, 2012; http://www.pharma-planta.net.

emerged from the European Commission's Framework Programme-funded project Pharma-Planta, creating a production system, approved by regulators, which can now be deployed as a flexible technology platform to produce other high-value proteins.

The European Cooperation in Science and Technology Framework (COST) Action on Molecular Farming (http://www.molecularfarming.org) has been very helpful in creating a European network to sustain and broaden the scientific basis of plant research to produce valuable molecules and to address the associated issues for clinical trials, regulatory approval and public acceptance. Main application areas within the COST Action cover proteins that may be required in large amounts (for example, monoclonal antibodies, subunit vaccines), medicines that can currently only be made in plants (for example, secretory immunoglobulin A antibodies) and medicines specifically designed for production in plants (for example, recombinant immune complexes engineered for enhanced immunological properties). Plant production systems in these areas offer various advantages in terms of scalability, cost-effectiveness, adaptability and speed.

It should be noted that in some of the case studies the technology does not use whole plants as the production system. Experience with cultured plant cells successfully overcomes many of the problems associated with production (Maxmen, 2012), in particular ensuring the fidelity with which it is possible to generate complex proteins appropriately glycosylated, folded and assembled, and free of the toxins that may complicate mammalian production systems. However, although plant cell culture systems may enjoy a shorter regulatory approval pathway (under the GMO Contained Use Directive, because transgenic material *in vitro* is isolated from the wider environment), and such systems do provide carefully controlled conditions, the cost of the product is significant by comparison with field-grown crop products (Wilson and Roberts, 2012)[33]. Therefore, the EU may again become increasingly uncompetitive, as other countries with their faster GMO regulatory frameworks transfer production of proteins from contained cell to field-scale systems. It has been proposed that broader and more balanced legislative oversight is needed if molecular farming is to advance in Europe (Sparrow et al., 2012).

Only a very small proportion of the large diversity of plant metabolites has been explored for production of novel therapeutics; there will also be many opportunities to produce small organic molecules as well as proteins. The increasing availability of high-throughput sequencing and interdisciplinary synthetic biology are transforming the discovery and production potential (De Luca et al., 2012). However, weaknesses in EU competitiveness arising from the translation from contained use to field scale may also be found to apply for those GM plant-based systems devised for other products (for example vanillin in food technology[34]).

4.8 Appreciating the new realities and addressing policy disconnects

This chapter has ranged widely in reviewing how the EU is becoming uncompetitive in the application of biotechnology-based approaches to agriculture, assessing the extent to which this is attributable to problems in devising and implementing proportionate regulatory systems. The implications for the science and technology base and public engagement, the need to respond to environmental challenges and the novel opportunities for innovation that are now coming within range, have all been emphasised.

We reiterate that crop genetic improvement technologies can only be part of the solution to the sustainable intensification of agriculture but it is unwise to exclude any validated tool, as EU policy may risk doing. Recent European Commission initiatives such as the Innovation Partnership on Agricultural Productivity and Sustainability (European Commission, 2012c) enable stakeholders to work together on shared objectives, offering an opportunity to transcend the entrenched positions that have impeded EU strategic development during the last two decades. The EU has much to do. There are rapid changes in the distribution of power in agriculture worldwide and the EU has retreated from world markets, '*… the export capabilities of the EU-27 in some key commodity sectors are predicted to decline further in the next 10 years, unless policy measures change markedly*' (Renwick et al., 2012). There is critical need to invest in R&D to find new ways to boost productivity (Renwick et al., 2012). The current EU research budget for agriculture is very small (less than 1%) compared with the CAP budget: a good case can be made to augment and coordinate this, for example through the Innovation Partnership, and to work harder to translate new knowledge to practice.

Based on the analysis in this and the preceding chapters, the EASAC Working Group highlighted several inconsistencies and disconnects across the current policy

[33] Because of the economies of scale-up, other current comparisons indicate that plant molecular farming can produce recombinant proteins at 0.1–10% of the cost of mammalian cell culture systems and microbial cell culture systems respectively (Chidambaram, 2011).

[34] In addition to the prospects for optimising synthesis of natural products in plant systems, synthetic biology is identifying ways to engineer plant systems to generate metabolites that they would not normally do and products that do not normally exist in nature (EASAC, 2010). This is a very active area of research in some Member States, for example the UK academic network Synthetic Plant Products for Industry (http://www.sppi-net.org/index.html).

landscape. Among these policy disconnects that need to be tackled are the following.

- Inconsistency whereby the EU may have approved the importation of food or feed of GM crop origin but has not approved the same GM crop for cultivation within the EU. This seems illogical and there will be other consequences of this policy disconnect: as other countries adopt less stringent regulations, there will be less incentive for them to make the investments to meet EU regulatory requirements for importation and, in consequence, the EU may experience increasing difficulty in accessing certain products.

- Inconsistency between the historical and current commitment to investment in plant sciences and the desire to promote a knowledge-based bioeconomy yet neglecting to use the outputs from research for agricultural innovation.

- Inconsistency between the objective to reduce chemical pesticide use and the over-regulation of alternative genetic approaches to protecting crops, such that it will become increasingly difficult to protect crops from pests and diseases.

- Inconsistency between the broad objectives of EU global development policy and the impact of EU GM practices on developing country decisions at a time when the EU agricultural footprint requires significant land use in developing countries to satisfy EU needs.

5 Conclusions and recommendations

The EASAC Working Group reached four main conclusions on the basis of its analysis in Chapters 2–4.

1. ***Land use and innovation.*** **The EU needs to increase its production and productivity of plant-derived biomass for food, feed and other applications, thereby decreasing dependency on imports and reducing its regional and global environmental impact. Commitment to agricultural innovation can be expected also to create jobs, benefit rural development and contribute to a growing gross domestic product. Biotechnology for crop improvement must be part of the response to societal challenges.**

In addition to achieving a higher proportion of its own food, feed and other requirements, the EU has a responsibility to help develop and use innovative agriculture to tackle global challenges. There is evidence that the EU is falling behind new international competitors in those applications, collectively termed crop genetic improvement technologies, for agricultural innovation. This will have implications for the EU science base, plant breeding capacity, farmers' income, competitiveness and growth as well as for food security, environment and the bioeconomy more broadly.

The impacts of climate change and other environmental and societal changes are likely to compound the challenges for food security. The current policy objective to reduce pesticide and other chemical use is likely to have adverse consequences for agriculture unless crops can be protected from pests and diseases in other ways, for example by conferring genetic resistance.

Science and technology will continue to be vitally important in driving agricultural innovation. GM techniques have revolutionised basic research in plants, leading to new understanding of processes such as disease resistance, photosynthesis, plant development and speciation. Applications of biotechnology for food and non-food crops can help to reduce reliance on non-renewable resources. Land sparing by efficient agriculture enables its use for other purposes within the EU, including conservation of biodiversity and carbon capture and storage in forests and permanent pastures. A more efficient EU agriculture will also enable more land in developing countries to be used for local needs.

Current legislation has slowed progress in the EU in developing new tools for a more sustainable and intensified innovative agriculture. This impediment must be addressed; the EU can be at the forefront of technology development and application to build both agriculture and environment that will be resilient to future challenges as well as providing coherent support for the bioeconomy.

This will not be possible without concomitant efforts to improve public awareness of the scientific, economic, environmental and strategic issues, to help to support better-informed individual choices, national political debate and EU priority-setting. The goal is to move from a situation where the passive consumer merely tolerates technologies to one where the active citizen appreciates and embraces technologies for the benefits they provide.

2. ***Regulation.*** **The trait and product not the technology in agriculture should be regulated, and the regulatory framework should be evidence-based.**

'*Regulations should help not hinder*' (House of Lords European Union Committee, 2010) and taking too precautionary an approach to new technologies poses risks to global food security. There is a need to unify and harmonise the regulatory and innovation-enabling roles of the EU policy-making institutions.

The specific physiological changes to plant function introduced by genetic modification are easier to characterise and assess than the less specific changes produced in other ways. When used appropriately and properly integrated within well-managed agronomic systems, GM crops can be economically, environmentally and socially beneficial. There is no validated evidence that GM has greater adverse impact on health and the environment than any other technology used in plant breeding. EU GM legislation was formulated when there was not yet sufficient data to substantiate these conclusions, but now there is. Given the experience gained, the legislation, data requirements and level of scrutiny need to be revisited and recalibrated.

As emphasised by EASAC in other areas of bioscience (EASAC, 2010; EASAC–JRC, 2011), all risk assessment must be evidence-based and should focus on the product not the technology. In the interim, a move to a trait-based regulatory system would facilitate simpler regulation for crop traits closely related to those already approved. Decisions on regulatory oversight have to be based on scientific principles and accumulated experience, and it is highly desirable to have consistent, proportionate regulatory regimes worldwide to facilitate both scientific exchange and trade. It is understandable why the present stringent GM regulatory framework was introduced originally into the EU even though, conceptually, it may not be defensible to suppose that one technology is intrinsically more in need of regulation than any other. As a general principle, it must be a science-based decision as

to whether surveillance and regulation are necessary and, if so, to what degree.

If the EU is to be competitive, it is also essential that regulation of the outputs of the New Breeding Techniques and molecular farming must have a firm foundation in sound science. Any risk of adopting a new technology must be compared with the risk of not adopting it and all innovation should be evaluated according to the same standards and principles.

3. ***Promoting competition.*** **The current expensive GM regulatory situation in the EU encourages monopolies.**

The EU regulatory framework should be reformulated to facilitate technology development, support commercial competition and generate diversity in innovation. The current domination of commercial GM practices by a few multinational companies is not simply a matter of patent rights or business practices but can also be directly attributed to the bureaucratic, time-consuming and expensive regulatory framework that deters all but the biggest companies. It is important to consider how best to stimulate open innovation practices to encourage smaller companies and public sector activities, to create the desired flexible and dynamic competition within the EU, and to avoid a relatively narrow genetic base that might compromise the attainment of food security.

It is vital that policy-makers learn lessons from the political and trade problems caused in the EU as a consequence of GM approval mechanisms. Plant breeding regulations should not hamper the interchange of science and technology or free trade.

4. ***The global context.*** **EU policy actions influence the developing world.**

The wider consequences need to be taken into account when deciding EU strategic options. Agricultural biotechnology can help to transform agriculture in African and other developing countries, if governments establish and use efficient regulatory systems. There is evidence that attitudes to GM in the EU have created difficulties for scientists, farmers and politicians in African and other countries. EU decision-makers need to be aware that inadvertent consequences of their policy choices can undermine the stated objectives of the EU agenda for international development and detract from EU efforts in capacity building. Therefore, reforming the current regulatory framework in the EU and creating necessary coherence between EU domestic objectives and a development agenda based on partnership and innovation is important for developing countries as well as for EU Member States and for elsewhere in Europe.

Recommendations

EASAC concludes that the potential benefits of crop genetic improvement technologies are very significant. Capturing these benefits in agricultural innovation should be a matter for urgent attention by EU policy-makers, alongside the development of indicators to monitor success in attaining the objectives (for example, for efficient and diversified land use). EASAC recommendations based on the four conclusions of the Working Group in the preceding paragraphs can be summarised as the following.

Regulatory framework. The European Commission should re-examine its current policy objectives and principles governing the broad area of agricultural biotechnology and should act in union with other frameworks, for example the integrated pest management strategies. As an immediate step, the European Commission together with Member States should consider further those process efficiency recommendations made in the external evaluation reports[35] but not yet implemented. The European Commission and the other EU Institutions should aim to achieve greater coherence in policy objectives and practices in protecting societal interests, to address the policy disconnects and inconsistencies discussed previously. The regulatory framework should be recalibrated to be science-based, transparent, proportionate and predictable, focusing on the trait and product, not the technology, and conforming to established timetables and evidence-based criteria for decision-making. The framework should take account of extensive experience gained, and good practice instituted, in regulating GM crops outside the EU. There must be an improved commitment to assessing benefits rather than focusing mainly on potential risk and uncertainty. The European Commission also needs to take a lead in discussions with Member States to reaffirm the cardinal principle that regulatory decisions and their implementation must be based on science. In addition there is need for urgent action to agree the status and regulation of New Breeding Techniques and, in particular, to confirm which products do not fall within the scope of GMO legislation.

Public engagement. The scientific community needs to maintain its commitment to engage with other stakeholder groups, including the food industry, media and NGOs and the public. Researchers must be proactive in clearly articulating the consequences of research findings and the opportunities and potential value in agricultural innovation, not just for GM crops but also for plant breeding more generally. Researchers need support from the academies of science in doing this. EASAC and its member academies will continue playing a significant

[35] DG Sanco (2011) GMO Evaluation, available at http://ec.europa.eu/food/food/biotechnology/evaluation/index_en.htm.

role in providing accurate and accessible messages to inform and sustain public debate and we will explore how the use of social media tools may help in communicating issues about food-related risk and benefits.

Research and development. The opportunities created by Horizon 2020, the European Research Council and European Research Area are extremely important in pursuing the priorities for plant sciences and agricultural biotechnology. The choice of biotechnology as a key enabling technology in Horizon 2020 is particularly welcome. However, there is an immediate need to ensure that biotechnology and the bioeconomy with regard to sustainable agriculture remains a priority in the current allocation of funding for Horizon 2020 research and its translation to innovation. Taken together with the work of the European Innovation Partnership on sustainable agriculture and simplification of the regulatory processes, these research initiatives can encourage the public sector and smaller companies to contribute to the knowledge-based economy. Specific research opportunities now coming within range have been noted in previous chapters, together with the importance of research in the social sciences to complement advances in the biosciences. One major priority for the research agenda is to model and anticipate the genetic adaptations that will be necessary for continued EU crop productivity as the climate changes. To assess whether or not particular combinations of physiological traits will enable adaptation to climate change, work to engineer such 'prototype' plants needs to start now, for testing performance under controlled conditions. In addition to the various specific research priorities there are four generic, infrastructural issues to tackle in support of promoting innovation.

- Identifying the skill requirements for the next generation of researchers and plant breeders; reversing the decline in some key scientific disciplines. Providing support for researcher career development to dissuade the permanent loss of skills to other countries can lead to increased employment in science in the EU.
- Revitalising public sector plant breeding efforts and improving opportunities for collaboration between the public and private research sectors with the translation of scientific outputs to agricultural practice.
- Clarifying the options for intellectual property protection, in particular relating to the co-existence between the systems of patenting and plant breeders' rights and stimulating open innovation.
- Increasing partnership between scientists in the EU and in developing countries.

International partnerships. The EU can learn from the rest of the world in characterising and implementing good regulatory practice while it must, in turn, also consider the impact of its policies on elsewhere in Europe and the rest of the world. The European Commission should explore new mechanisms for sharing experience and engaging in international research with emerging economies demonstrating growing scientific strengths, to support their capacity-building and progress mutual interests in sustainable agriculture. The academies of science and their regional networks have key roles in identifying and pursuing priorities for the crop genetic improvement technologies, within their countries and on a regional basis. The EU academies of science should continue to work with their colleagues in the African and other academies to tackle goals informed by local strengths, needs and priorities. EASAC will continue to discuss with other academies how to pursue relevant issues for coordinated policy at the global level.

There is need to create better coherence in policy to exploit the technologies that the EU was instrumental in generating. The EU has the potential and the responsibility to take a leading role in providing and using scientific solutions to improve agricultural productivity and to reduce the adverse impact of agriculture on the environment. EASAC is ready to continue playing its part in catalysing discussion of the issues and exploration of the opportunities and challenges.

Appendix 1 Working Group

The report was prepared by consultation with a Working Group of experts acting in an individual capacity, nominated by member academies of EASAC:

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The Working Group started in April 2012 and completed its work in April 2013. The report was independently reviewed by additional experts nominated by EASAC. The analysis of comparator countries in Chapter 2 and Appendix 3 was discussed with the academies of science in the relevant countries. Chapter 3 was prepared by drawing on collaboration with NASAC and was informed by discussion in a workshop in November 2012 (see Appendix 5).

Appendix 2 Relevant previous publications by member academies of EASAC

Among the recent EASAC-academy publications are the following.

- Comprehensive accounts from the academies of sciences in the Czech Republic (Sehnal and Drobnik, 2009) and Hungary (Agriculture section of the Academy, Balazs et al., 2011) reviewing national scientific strengths, potentially undermined by the principles, precepts and practicalities of the EU approach to regulating GM crops.

- Discussion between academicians in the Academie des Sciences in France (2010), addressing the question of whether GMOs pose a threat to biodiversity. The consistent message in this work is that, on the contrary, current evidence indicates that GMOs are of real benefit from an environmental perspective in encouraging genetic diversity, and that GMO research should continue. A new report on GMOs will be published in 2013.

- A statement on behalf of the Union of German Academies of Sciences and Humanities (German National Academy of Science Leopoldina et al., 2009) urges policy-makers to demonstrate leadership in creating a science-based framework for management of innovation in agriculture, accelerating approval procedures and explaining to the consumer the wide range of possibilities opened up by genetic modification technology, including extending the ecological growth zone of cultivated plants and promoting biodiversity.

- In its report, the Royal Society (2009) also marshals a broad array of evidence to make the case for the part played by biosciences, including biotechnology, in the sustainable intensification of global agriculture in which yields are increased without adverse environmental impact or cultivation of more land. In discussing the principles underlying the governance of new technologies, the Royal Society emphasised that regulation to assess benefits, risks and uncertainties must be science-based, proactive and proportionate, seeking to build on a shared vision of societal objectives for agricultural sustainability.

- Further discussion of the role of the EU in contributing to the global sustainable intensification of agriculture to achieve food security is provided in the Warsaw Consensus Statement produced by the Polish Academy of Sciences (2011). The Biotechnology Committee of the Polish Academy of Science is a strong supporter of the use of GMOs for industry and agriculture (Weglenski and Twardowski, 2012).

- A report released by the Swiss Academies of Arts and Sciences (Swiss Academies, 2013) concludes that GM crops can contribute to an environmentally sustainable and productive agriculture in Switzerland.

Appendix 3 Background information on comparator countries

1 Argentina

1.1 Status

Argentina first adopted GM crops in 1996 (glyphosate-tolerant soybean), and within four growing seasons nearly 100% of the soybeans planted were GM. Soybean production increased dramatically during this time, from 12 million tonnes produced in 1996 to 52 million tonnes produced in 2010 (FAOSTATS). Over 22 million hectares have been planted with GM soybeans, maize and cotton since the country first commercialised the technology. GM crops account now for nearly all soybeans and cotton crops, and 86% of maize crops (Trigo, 2011).

In 2012 Argentina approved the second-generation GM soybean, which combines herbicide tolerance with a gene reported to drive higher yields[36]. With this approval the number of GM events authorised for cultivation reached 28. Since GM crops were first adopted, a major trend has been a shift from use of varieties with single traits to those with combined traits.

The GM technologies approved so far for commercial cultivation and for contained field trials are of foreign origin. The similarity between the agro-ecological conditions in which GM crops were developed and those where they were to be grown commercially facilitated their rapid uptake in Argentina (Trigo, 2011).

1.2 Regulation

The responsibility of granting approvals for GM events lies within the Argentinean Ministry of Agriculture (MinAgri). The process requires contributions from three institutions[37]. Decisions are based on (1) environmental risk evaluation, (2) food and safety assessment and (3) analysis of the potential impacts on international trade for Argentina.

The 'mirror policy' in the approval of GM crops in Argentina takes into account the state of play of export markets with regard to GM regulations, and in particular, the EU and more recently, India and China. This means that only those events already approved in key export markets are granted approval (Vicien, 2012). The inclusion of a mandatory socio-economic impact assessment, comprising an *ex ante* assessment of the economic impact on trade and competitiveness, is a feature of the Argentinean approval system. This is aimed at guiding political and strategic choices with respect to international trade (Vicien, 2012).

1.3 Research

Public agricultural research in Argentina is largely financed by the national government, and carried by the Argentinean National Agricultural Technology Institute, INTA (Instituto Nacional de Tecnología Agropecuaria). Agricultural R&D in Argentina has become increasingly demand driven with funding delivered through competitive schemes. Research activity has played a key role in stepping up the country's agricultural production and exports over the past decade.

Public agricultural research using advanced genetic techniques is largely under INTA's Strategic Area '*Genetic Resources, Genetic Improvement and Biotechnology*'[38], which includes the research initiative '*Capacity Building for the Production of Transgenic Organisms*'. Projects in this initiative include the following.

- Development and adaptation of tools for plant genetic transformation of agricultural species of interest. Transformation protocols are being developed for local cultivars of woody perennial species including willow, vine, cotton, sunflower, wheat, maize, onion and garlic.
- Generation of vaccines and antibodies in transgenic plants: from concept to product. Aims include production at a pre-industrial scale of a vaccine in alfalfa against Newcastle disease virus; generation of three complex antibodies (against the VP6 capsid protein of rotavirus type A; an antibody against the VP8 protein of the simian rotavirus, and the secretory versions of these in tobacco and tomato plants); and production of recombinant antibodies in potato against infectious bursal disease and Newcastle disease.
- Molecular breeding for forage species for restrictive environments. Agriculture has displaced livestock production from the Pampas to new areas of different

[36] http://www.minagri.gob.ar/site/institucional/prensa/index.php?edit_accion=noticia&id_info=120822171448.

[37] The institutions involved are the Advisory Commission on Agricultural Biotechnology (Comisión Nacional Asesora de Biotecnología Agropecuaria – CONABIA), which evaluates agricultural and environmental impacts through trials; the National Agrifood Health and Quality Service (Comité Técnico Asesor sobre uso de Organismos Genéticamente Modificados del Servicio Nacional de Sanidad y Calidad Agroalimentaria -SENASA), responsible for food safety evaluation; and the National Directorate for Agrifood Markets (Dirección Nacional de Mercados Agroalimentarios) which evaluates potential commercial impact focusing on export markets (Burachik and Traynor, 2002; Lusser et al., 2012).

[38] On the *Strategic Area of Genetic resources, Breeding and Biotechnology*, INTA seeks to create knowledge and tools for the characterisation and generation of genetic variability to assist plant breeding programmes and the development of biotechnology products. Information on current projects is available in the INTA website: http://inta.gob.ar/proyectos/aerg.

agro-climatic conditions, and therefore forage species adapted to these new environments need to be developed. This project includes the generation of GM fescue (*Festuca arundinacea*).

- Obtaining GM plants tolerant to biotic and abiotic stresses. Main areas of research are: control of fungal diseases in alfalfa, wheat and potatoes; control of viral diseases in potato; and increased tolerance to abiotic stresses in species of national economic importance (alfalfa, wheat, maize and soybean).

2 Brazil

2.1 Status

In 2012 Brazil planted over 36 million hectares of GM soybean, maize and cotton (James, 2012). Brazil is the second largest (by volume) exporter of soybeans in the world after the USA; the crop is substantially of GM origin. Soybean production in Brazil increased from 23 million tonnes in 1996 to 69 million tonnes in 2010, and in 2010 Brazilian soybeans exports exceeded US$11 billion (FAOSTATS).

Eight GM events were approved in 2010, six in 2011 and three in 2012[39]. New approvals consist mostly of stacked tolerances to several herbicides in soybean, maize and cotton, and combined herbicide and insect resistance in maize and cotton. One of the GM events approved in 2009 was tolerance to imidazoline herbicides developed by Embrapa (Empresa Brasileira de Pesquisa Agropecuária, the Brazilian Enterprise for Agricultural Research[40]) and present in a GM soybean variety. This was a collaboration between Embrapa and a multinational company[41]. Embrapa also developed a GM bean variety with resistance to bean golden yellow mosaic virus, which was approved in 2011[42]. This GM bean is the first transgenic crop entirely produced by a public research institution[43] (Aragão and Faria, 2009). Brazil is the second largest producer in the world of dry beans after India (FAOSTATS), and production in 2010 was estimated at US$1.8 billion (FAOSTATS). This legume is the main vegetable source of protein and iron in the country. Bean golden yellow mosaic virus causes one of the most serious viral diseases of beans and results in severe production losses (Morales and Anderson, 2011).

In 2011, a Brazilian forestry, pulp, paper and renewable energy company received approval for its fourth and final regulatory field trial for yield-enhanced GM eucalyptus[44].

2.2 Regulation

In 2003, the Brazilian Congress passed a law on biosafety (Bill 2401). This ended the long-standing, illegal plantings of GM soybean using seeds imported from Argentina, mitigated by the 1-year edition of specific Provisional Measures allowing for the cultivation of transgenic soybeans (Schnepf, 2003; da Silveira and Borges, 2005). The Bill was replaced by the current Biosafety Law (11.105/05[45]), enacted in 2005, which established the terms of the regulation of all aspects of handling and use of GMOs in Brazil, including research, contained field trials, transportation, imports, production, storage and marketing.

The National Technical Commission on Biosafety (Comissão Técnica Nacional de Biossegurança (CTNBio)) is a multidisciplinary consultative body established under the Ministry of Science and Technology to provide technical and advisory support to the Federal Government for the implementation of the national biosafety policy. Activities with GMOs are only allowed in established institutions after authorisation by CTNBio. In 2011 CTNBio also published new standards for monitoring GMOs after their release into the market.

Institutions dealing with GMOs are also required to establish an Internal Biosafety Commission (Comissão Interna de Biossegurança (CIBio)), with a designated lead researcher. CIBios are essential components for monitoring and surveillance of the research, handling, production and transportation of GMOs, and are responsible for enforcing biosafety regulations.

2.3 Reported impact of GM crops and implications for policies

Contrary to the situation in Argentina, the increase in scale in soybean farming operations in Brazil largely pre-dated the adoption of GM crops (Goedert, 2006; Bindraban et al., 2009). In Brazil, soybean was traditionally grown in the south in smallholder

[39] The list of approved events is available at http://cib.org.br/biotecnologia/regulation/ctnbio/brazilian-commercial-approvals/.
[40] The foundation of Brazil's research system is Embrapa (http://www.Embrapa.br/), a semi-autonomous body under the Ministry of Agriculture, Livestock, and Food Supply (MAPA) with the mission of providing technological solutions for sustainable agricultural development in Brazil (da Silveira and Borges, 2005). Since 1992 Embrapa is responsible, in cooperation with other research institutions and universities, for coordinating the National Agricultural Research System (Sistema Nacional de Pesquisa Agropecuária, SNPA; http://www.embrapa.br/a_embrapa/snpa).
[41] http://cib.org.br/biotecnologia/regulation/ctnbio/brazilian-commercial-approvals/ and http://www.embrapa.br/imprensa/noticias/2010/fevereiro/1a-semana/soja-cultivanceae-da-basf-e-da-embrapa-recebe-aprovacao-para-cultivo-comercial-no-brasil/.
[42] http://cib.org.br/biotecnologia/regulation/ctnbio/brazilian-commercial-approvals/.
[43] http://www.cenargen.Embrapa.br/_comunicacao/2011/cenargenda/cenargenda62_en_2011.html
[44] http://www.futuragene.com/Futuragene-Brazil-field-trials.pdf.
[45] The law can be accessed at http://cib.org.br/wp-content/uploads/2012/02/LeiDeBiosseguranca.pdf.

production systems, but production expanded to the Cerrado region in the 1970s, mostly on large farms with high levels of mechanisation which replaced areas of grass and scrub savannah (Goedert, 2006). A more recent trend is the expansion of soybean production in northern states in recently deforested lands (including the Amazon area; Cerri et al., 2005; Kessler et al., 2007). No-till agriculture has been adopted widely since the 1980s (Bolliger et al., 2006).

All of the considerations pertaining to the sustainability of soybean production in large-scale farm-holdings as monocrops (listed above for Argentina) also apply in Brazil. An additional problem encountered is the development of glyphosate-resistant weeds (Cerdeira et al., 2007, 2011; Christoffoleti et al., 2008; Bindraban et al., 2009; see section 2.5.1.3). The development of herbicide resistance is, however, not a consequence of the use of GM technology as tool in plant breeding but rather is a consequence of the production system and the agricultural practices deployed.

A review of the studies on the economic and environmental impact of GM soybean in Brazil concluded the following: GM soybeans do not significantly increase yield per hectare; the economic gain from herbicide-tolerant soybeans is minimal; GM soybean is easier to manage than conventional crops (but this is more significant in large-scale farms); the use of herbicide in GM soybean cultivation increased, although this may be compensated by the lower toxicity of glyphosate (Silveira and Borges, 2005); and gene flow from GM to conventional varieties does not represent a significant risk (Pereira et al., 2007, 2012).

In terms of the environmental impact of Bt cotton, Embrapa scientists have tested the effect of GM cotton on non-target insect species (Moraes et al., 2011, Sujii et al., 2013) and rats (Guimarães et al., 2010), and studied the likely impact of gene flow (Abud et al., 2007). These studies reported no negative effects related to the use of Bt cotton.

The '*BioSeg- biosafety of GMOs*' research initiative[46] aims to characterise the biosafety of GM crops developed by Embrapa. It will focus on soybean, potato resistant to potato virus Y, virus-resistant bean, papaya resistant to papaya ringspot virus, and Bt cotton.

3 India

3.1 Regulation

The Rules for the Manufacture, Use, Import, Export and Storage of Hazardous Microorganisms/Genetically Engineered Organisms or Cells were issued in 1989 by the Ministry of Environment and Forests under the Environment (Protection) Act, 1986. These rules also define the competent authorities and their composition for handling of various aspects of the rules: the Recombinant DNA Advisory Committee (RDAC), the Institutional Biosafety Committee (IBSC); the Review Committee on Genetic Manipulation (RCGM); the Genetic Engineering Appraisal Committee (GEAC); the State Biotechnology Coordination Committee (SBCC); and the District Level Committee (DLC). The RCGM, established under the Department of Biotechnology, supervises research activities including small-scale field trials, whereas the GEAC[47] is responsible for granting approvals for large-scale releases and commercialisation of GMOs. The Rules also mandate that every institution engaged in GMO research establish an IBSC to oversee such research and to liaise with the RCGM.

3.2 Research

India has substantially increased its public funding of agricultural research since the late 1990s, and during the 2000–07 period the growth in public agricultural R&D was 25% (Pal et al., 2012). Nonetheless, India's research intensity ratio, measured as public agricultural R&D spending as a share of agricultural output, continues to be relatively low, and agricultural growth continues to lag behind the target 4%. The Indian government has pledged 1% of agricultural gross domestic product to agricultural R&D to redress this shortcoming.

The Indian public agricultural research system has two tiers. At the federal level the first tier comprises mainly a network of nearly 100 institutions coordinated by the Indian Council for Agricultural Research (ICAR). The second tier consists of a system of state agricultural universities acting at the regional level (Pal et al., 2012). ICAR is responsible for planning and coordinating agricultural research and education in the country, and it accounts for more than half of India's public agricultural R&D spending and about one-third of the country's agricultural researchers. The largest institute in the ICAR system is the Indian Agricultural Research Institute and in 2009, 50% of the FTE researchers employed by the government performed crop research (Pal et al., 2012).

ICAR also supports the Krishi Vigyan Kendras, a network of small teams that perform agricultural extension activities and assist in tailoring technology recommendations and demonstrating them on farmers' plots.

Although the quality of India's research staff has improved, the number of researchers has fallen by 8% since the turn of the millennium. This drop is primarily driven by declining research capacity at the state agricultural universities owing to budget constraints. Without an effective policy

[46] http://www.Embrapa.br/programas_e_projetos/pesquisa-em-rede/folhetos/Bioseg.pdf.
[47] http://moef.nic.in/modules/project-clearances/geac-clearances/.

response, the state research capacity will decline further. The focus of agricultural research in India has widened and become more complex, and notwithstanding the rising trend in government funding for agricultural R&D, more resources will be needed to meet the needs of the growing population (Byerlee and Pal, 2006).

Private-sector participation in agricultural R&D is dominated by companies involved in breeding, biotechnology, animal health, plant protection and farm machinery. Since the mid-1990s, agricultural R&D spending by the private sector has increased fivefold (Pray and Nagarjan 2012), and in 2008–09, private sector accounted for 19% of India's total investment in agricultural R&D. Biotechnology is one of the fastest growing, knowledge-driven industries in India. Indian biotechnology industry registered over US$3.0 billion revenue generation in 2009–10, which constitutes about 2% share of the global biotechnology market (Malhotra et al., 2012). Although biopharmaceuticals is the largest biotechnology sector in India, bioagriculture recorded the highest growth in 2009–10, dominated by insect-resistant transgenic cotton (Malhotra et al., 2012).

4 Australia

4.1 Status

Australia has approved GM cotton and GM oilseed rape for cultivation. GM cotton has been grown since 1996 and now constitutes approximately 95% of Australia's cotton crop (Australian Department Agriculture, Fisheries and Forestry, 2012).

Two varieties of GM oilseed rape were approved for commercial production in 2003, but moratoria on cultivation were enacted in the main oilseed rape producing states owing to market access concerns. Consequently, GM oilseed rape was first grown commercially in 2008 in the states of Victoria and New South Wales, and Western Australia allowed the commercial planting of GM oilseed rape only in 2010[48]. In 2010 around 130,000 hectares of GM oilseed rape were planted, representing around 8% of the total crop in Australia. Tasmania has a moratorium on the commercial release of GMOs until 2014, and South Australia's moratorium on GM food crops will continue until at least 2019.

4.2 Regulation and strategic directions

In Australia each genetic trait is individually assessed on a case-by-case basis by the Office of the Gene Technology Regulator (OGTR), the Food Standards Australia New Zealand (FSANZ) and the Australian Pesticides and Veterinary Medicines Authority (APVMA)[49]. The Office of the Gene Technology Regulator oversees the development and environmental release of GMOs, under the Gene Technology Act 2000 and corresponding state and territory legislation. The Gene Technology Amendment Regulations (2011) sought to increase the effectiveness of the legislation, facilitate compliance and ensure the regulation of GMOs remains commensurate with risk levels and current scientific understanding. Decisions on whether to allow GM crop production in part or all of a state or territory are a matter for that jurisdiction.

The Food Standards Australia New Zealand (FSANZ[50]) is a bi-national Government agency with the main responsibility of developing and administering the Australia New Zealand Food Standards Code, which lists requirements for additives, food safety, labelling and GM foods[51]. Enforcement and interpretation of the Code is the responsibility of state/territory departments and food agencies within Australia and New Zealand.

Towards a National Food Plan for Australia: the Green Paper. The Australian Government (DAFF, 2012) has set out to develop the National Food Plan, a framework to define its role in the food system, through a consultative policy development process involving circulation of an issues paper, followed by a green paper for stakeholder comment, concluding with the release of a National Food Plan white paper that articulates its policy position[52]. One of the aims of the exercise is to develop a national strategy on the consistent application of modern biotechnology in agriculture, including genetic modification for crop improvement.

The areas, highlighted by the Green Paper, where modern technologies for food production (including GM) can have a significant impact are (1) food production for food security (including improved nutritional qualities of food for a healthy and balanced diet), (2) competitiveness in international trade in food commodities and (3) mitigation of climate change, in particular coping with drought.

Australian competitiveness in international food trade: the 'Asian century'. Australia is a major agricultural commodities exporter and it competes with emerging economies (Brazil, Argentina, India and China) for markets. World food demand is expected to rise by 77% by 2050. Forty per cent of Australia's annual farm and fisheries production is exported to Asia, and the

[48] http://www.daff.gov.au/agriculture-food/biotechnology.
[49] http://www.daff.gov.au/agriculture-food/biotechnology/framework.
[50] http://www.foodstandards.gov.au/.
[51] For a list of applications and status of approval of GM crops by June 2012 visit http://www.foodstandards.gov.au/consumerinformation/gmfoods/gmcurrentapplication1030.cfm.
[52] More information on the consultation is available at http://www.daff.gov.au/nationalfoodplan/process-to-develop/green-paper/stakeholder-consultation.

total value of food exports (2010–11) was 27.1 billion Australian dollars. Australia is hence very well positioned to increase share of exports to satisfy increased food demands in Asia due to population increase and change of diets. The government proposes a target of doubling the value of food exports by 2030.

A report produced by the Australian Bureau of Agricultural and Resource Economics (Acworth et al., 2008) presented a quantitative assessment of the potential economic benefits of further GM crop adoption in Australia at the regional and state levels. Crops considered included canola, soybean, maize, wheat and rice. The report concludes that delaying GM crop uptake in Australia while emerging economies continue to increase uptake will have adverse impacts on Australian exports. In the simulations, the adoption of GM crops is estimated to benefit the Australian economy even in the scenario where GM crops are restricted in foreign markets (such as the EU; Acworth et al., 2008).

4.3 Research

The Australian Government's total investment in science, research and innovation was estimated at $9.08 billion in 2010–11, up from $4.97 billion in 2002–03 (DAFF, 2012). Australia's national science organisation, the Commonwealth Scientific and Industrial Research Organisation (CSIRO), has a portfolio of research programs across the entire food chain, from farm to consumer. In 2011–12, CSIRO's total investment in food, health and life sciences research was estimated to be approximately $337 million, including external revenue of about $137 million[53]. Research supported by CSIRO has to be aligned with the priorities of one or more of the National Research Flagships[54].

Food Futures[55] is the National Research Flagship aimed at increasing the ability of Australia to produce clean, healthy foods efficiently. By applying frontier technologies to high-potential industries, the Flagship's goal is to add 3 billion Australian dollars annually of value to the Australian agricultural food sector. *Future grains, grain based foods and feed*[56], one of the three key research areas of the Food Futures Flagship, applies advanced genetics to develop novel, high-value grains and oilseeds.

Main initiatives include the following:

- CSIRO formed a public–private partnership with an international company to increase yield in wheat through genetic modification. CSIRO has developed a wheat variety that produces significantly more grain (up to 30% increase in yield in glasshouse trials) and the partnership aims to bring this technology to the market.

- Arista Cereal Technologies is a joint public–private venture with an European company aiming to deliver new high-amylose wheat varieties developed using RNAi gene silencing techniques to suppress two of the key genes involved in starch formation. The new wheat features a high proportion of amylose (an increase from 25 to 70% compared with conventional varieties), a slowly digested form of resistant starch that can be used to formulate foods with a low glycaemic index. Consumption of these grains is expected to reduce the incidence of diet-related conditions such as type 2 diabetes, obesity, cardiovascular disease and colorectal cancers (Regina et al., 2006).

- The High Fibre Grains Collaboration Cluster combines the research capabilities of the three Australian universities to develop healthy complex cereal carbohydrates. Genetic manipulation strategies are used to optimise the content and composition of the major cell wall polysaccharides, the largest source of grain fibres. The cluster will generate elite transgenic events and parental non-transgenic germplasm capable of effective and rapid commercialisation through industry partnerships. Research will focus on wheat, barley and rice.

- CSIRO have joined forces with the largest European wheat seed company to commercialise nitrogen use efficiency wheat in Australia.

- A public–private research collaboration aiming to develop through genetic manipulation oilseed varieties with high-quality long chain omega-3 oils containing docosahexaenoic acid, traditionally only found in ocean-based algae and fish (Venegas-Calerón et al., 2010; Petrie and Singh, 2011; Petrie et al., 2012). The initiative aims to be trialling elite lines as early as 2013 and have seeds commercially available by 2016. These varieties would break the world's reliance on fish for these oils.

Wheat and oilseed rape are two key crops for European agriculture. It is noteworthy that most of the initiatives described above rely on fundamental research performed in European laboratories (Sun et al., 1998; Regina et al., 2006; Venegas-Calerón et al., 2010) and which will be

[53] http://daff.gov.au/__data/assets/pdf_file/0009/2175156/national-food-plan-green-paper-072012.pdf.
[54] http://www.csiro.au/en/Organisation-Structure/Flagships.aspx.
[55] http://www.csiro.au/org/FFF-overview.
[56] The goal of Food Futures is to transform the international competitiveness of the Australian agrifood sector, adding 3 billion Australian dollars annually, by applying frontier technologies to high potential industries. Please refer to the website for additional information on specific projects: http://www.csiro.au/Organisation-Structure/Flagships/Food-Futures-Flagship.aspx.

deployed in Australia in collaboration with European seed industries. EASAC strongly believes the EU should also aim to benefit from scientific advances originating from research investments, and capitalise from the high quality of European plant sciences research to solve constraints to agricultural productivity in the continent.

5 Canada

5.1 Status

Canada is the fourth-largest producer in the world of GM crops. In 2012, Canada commercially planted 11.6 million hectares of GM oilseed rape, maize, soybean and sugar beet (James, 2012). GM oilseed rape was grown on 8.4 million hectares (nearly all planted oilseed rape was of GM origin). Canada has approved over 120 GM events[57].

The types of novel trait tested in research trials since 1988 include herbicide resistance, resistance to insect pests or plant pathogens, pollination control mechanisms, stress tolerances, changes in nutritional quality, and production of high-value substances, such as pharmaceuticals and industrial chemicals. The species involved include *Brassica* species, potatoes, corn, flax, soybeans, wheat, safflower, alfalfa, lentils, sugar beet, barley, broccoli, canary seed, grape vine, pea, perennial ryegrass, poplar, tobacco, tomato, white clover and several tree species. More than 8000 confined trials of over 1000 unique PNTs have been authorised in Canada since 1988, and 858 field trials took place in 2011 alone (Thomas and Yarrow, 2012; and [58]).

5.2 Reported impact of GM crops and implications for policies

The changes in oilseed rape seed led to an area increase from less than a half million hectares in 1968 to more than 8 million 2012, and from less than 5% of crop land in Canada to over 30% (Agriculture and Agri-Food Canada 2012; James 2012; Brewin and Malla, 2013). Canada is the largest exporter in the world of oilseed rape (FAOSTATS). There has been a shift from public to private investment in research on oilseed rape: before 1970s almost all the research was in public institutions, whereas in 2012 a few firms dominated investment on oilseed research (Brewin and Malla, 2013). Before 1995, the dominant varieties in terms of area were all developed by public institutions whereas from 1995 to 1998, 88% of the 104 varieties registered were private.

Overall, the benefits from adopting GM oilseed rape are reported to be significant (Phillips, 2003; Serecon Management Consulting, 2005; Gusta et al., 2011), although the conclusion of an earlier study was that a proportion of adopting farmers benefit from the technology, but not all (Fulton and Keyowski, 1999). At currently seeded areas and seed prices, producer benefits were estimated to be more than $1 billion and breeding firm returns were more than $700 million (Brewin and Malla, 2013). These benefits come from the agronomic benefits of new herbicide-tolerant varieties as well as the gain in productivity from improved breeding and hybridisation (Veeman and Gray, 2010).

5.3 Research

Agriculture and Agri-Food Canada's (AAFC's) Science and Innovation Strategy[59] was developed in 2006 and it identifies a broad vision for the sector. The five-year *Growing Forward 2* policy framework will streamline investments in the agriculture and agri-food sector. The new agreement represents a $3 billion investment, including a 50% increase in governments' cost-shared investments in innovation, competitiveness and market development. Starting in 2013, the following three new federal programs will make investments to strengthen further the sector's capacity to grow and prosper:

- The AgriInnovation Program will focus on investments to expand the sector's capacity to develop and commercialise new products and technologies;
- The AgriMarketing Program will help industry improve its capacity to adopt assurance systems, such as food safety and traceability, to meet consumer and market demands. It will also support industry in maintaining and seizing new markets for their products through branding and promotional activities;
- The AgriCompetitiveness Program will target investments to help strengthen the agriculture and agri-food industry's capacity to adapt and be profitable in domestic and global markets.

[57] The database listing containing information on the status of regulated plants with novel traits in Canada, including whether products have been approved for unconfined environmental release, novel livestock feed use, variety registration and novel food use is available at http://active.inspection.gc.ca/eng/plaveg/bio/pntvcne.asp.
[58] The summary of Submissions and Field Trials of Plants with Novel Traits (PNTs) Proceeding under the Seeds Act, 2011, is available at http://www.inspection.gc.ca/english/plaveg/bio/st/st_11e.shtml (last accessed 21 February 2013).
[59] See www.agr.gc.ca for more information. Based on the 2005 Science Consultations, the Department has developed a new Agriculture and Agri-Food Canada (AAFC) Science and Innovation Strategy that identifies seven priorities of national importance where AAFC will play a leadership role. These are outlined in http://www4.agr.gc.ca/AAFC-AAC/display-afficher.do?id=1183760559460&lang=eng.

Appendix 4 Methodological difficulties in measuring the socio-economic impact of GM crops

GM has been described as the agricultural technology with the most rapid rate of adoption in history but it is also the most controversial technology in the history of plant breeding. The reason for this is not only because it is a very powerful tool for increasing the speed and scope of crop improvement but also both the technology and its applications have become proprietary. The first generation of commercially exploited GM crops were brought to the market by large multinational companies. In addition, GM crops have become associated with large industrial-scale agriculture and monoculture cultivation despite the fact that these agronomic choices are entirely unrelated to GM technology *per se*. All these factors have raised societal and even ethical concerns about the use of GM crops and particularly their impact on small-holder farmers in developing countries.

Many studies of the socio-economic and environmental impact of cultivation of GM crops have been published since the technology was adopted (reviewed in Brookes and Barfoot, 2009; Carpenter, 2010, 2011; Finger et al., 2011; Areal et al., 2013; and see Chapters 2 and 4 of the present report). A meta-analysis (Finger et al., 2011) has examined the effects at farm level of growing insect-resistant GM crops using published data from more than a decade of field trials and surveys. This work indicated that, at a global scale, GM crops can lead to yield increases and to reduced pesticides used, whereas seed costs are usually substantially higher than for conventional seed varieties. Growing GM and non-GM crops in the same area has also been reported to be beneficial for non-GM crops[60].

The nature and magnitude of effects from cultivating GM crops do, however, differ between countries and regions, particularly because of differences in pest pressure and pest management practices. Published accounts are skewed towards some countries, and individual studies rely on different assumptions and were conducted from different purposes. In addition, short-term studies (focusing on one or two growing seasons) may not necessarily reflect long-term impacts of adoption, especially because unobserved costs that may arise with the cultivation of GM crops (such as effect on land rents, longer-term market responses, governmental regulation and public acceptance) are difficult to predict and quantify. For these reasons, the selection of single studies can be used as evidence in support of a particular view about GM technology when the whole picture from the composite of evidence is rather different. There has been selective use of evidence on both sides of the debate but this has little to do specifically with the technology of GM, more the outcomes from specific applications in particular circumstances (Finger et al., 2011).

The polarisation of the GM debate may also have influenced the choice of methodologies used for analysis (Smale, 2012). A study of peer-reviewed articles on the socio-economic impact of cultivation of GM crops in developing countries analysed 321 articles covering the subject (Smale, 2012). In terms of content, about half of the studies examined the impact on farmers (other actors in the value chain are underrepresented), and most studies focused on Bt cotton. The ratio of review articles to primary analyses is high, and the number of socio-economic impact assessment studies has declined in recent years. The most common methodologies used are partial budgets, followed by farm production and input use models (Smale, 2012). The main limitation of these studies resides in the quality of the datasets used (Smale, 2012). Data sources are generally farm surveys, trial data, or company data. Some studies are based on several datasets, and early studies were typically based on very small samples. Conceptual limitations of early studies include the presentation of gross rather than net margins, which fails to take account of land or labour costs. These early studies did not address the bias associated with the self-selection of farmers growing GM crops (in general, farmers who are better informed or with more resources are more likely to adopt new technologies); self-selection bias was only taken into account in studies from 2007 onwards (Smale, 2012).

Several studies have also highlighted the importance of local political and economic institutional arrangements that constrain farmers' choices and of the social nature of decision making in the adoption of new technologies (Witt et al., 2006; Stone, 2007). Adoption rates are therefore not necessarily indicative of the success or acceptance of agricultural innovations. These accounts stress the difficulty of interpreting socio-economic impact assessment data without careful consideration of the ecological and political or economic context in which the new technology was introduced.

[60] The cultivation of GM papaya resistant to Papaya Ringspot Virus in Hawaii lowered the incidence of the virus and allowed farmers again to grow non-GM fruit trees (Fuchs and Gonsalves, 2007). Similarly, the adoption of Bt cotton in China was reported to reduce the incidence of cotton borers in other host crops in the same area (Wu et al., 2008). See Chapter 4 for further discussion.

Appendix 5 Perspectives from African countries on innovation in agricultural biotechnology

In November 2012, NASAC and EASAC helped to co-organise a workshop together with ATPS, the African Technology Policy Studies network, and with support from the John Templeton Foundation and the Malaysian Cambridge Studies Centre (MCSC).

We would like to thank the MCSC and the John Templeton Foundation for the small grants that helped support this workshop on perspectives from African countries. The opinions expressed in this publication are those of EASAC and do not necessarily reflect the views of the John Templeton Foundation.

This workshop provided an opportunity for academy-nominated scientists to describe what is happening in African agricultural biotechnology today, what are the objectives for the future and how relationships with the EU might be promoted. This appendix summarises four presentations from the NASAC academy-nominated scientists together with points raised in general discussion by an audience of NASAC, EASAC and ATPS scientists. Further information on other presentations in this and other sessions is available from http://www.atpsnet.org/media_centre/news/article.php?article=122 (ATPS annual conference and workshops "Emerging Paradigms, Technologies and Innovations for Sustainable Development: global Imperatives and African Realities").

Presentations

1. W. Alhassan (Forum for Agricultural Research in Africa, Accra, Ghana), '*Current situation in GM research and innovation on Ghana and the sub-region: opportunities and challenges*'

West Africa is a food insecure region, home to one in four of the world's under-nourished people. The application of known technologies in agriculture coupled with modern biotechnology, governed by a legislative framework that generates an acceptable level of security, is needed to increase farmers' productivity.

In Burkina Faso, Bt cotton cultivation has provided proof-of-concept to demonstrate that biotechnology works. Current R&D in confined field trials is assessing Bt cowpea (to tackle major pests, notably the Maruca cowpea borer) and biofortified sorghum. In Nigeria, biofortified cassava (supplementary carotene and iron) and locally developed cultivars of Bt cowpea and biofortified sorghum are in R&D, also in confined field trials. In Ghana, following implementation of a comprehensive Biosafety Law as enabling legislation, candidate GM crops pending approval are *Maruca*-resistant cowpea, nitrogen- and water-use efficient, salt-tolerant rice and high-protein sweet potato. Subsequent to the November 2012 Addis Ababa meeting, permits for confined field trials for these crops have been granted. According to farmer-defined needs, there is also high future potential in Ghana for GM cassava, black-sigatoka-resistant banana and plantain, coconut resistant to lethal yellowing disease, and cabbage resistant to diamond back moth.

To promote R&D and implement innovation across the region, momentum has to be maintained in tackling key challenges:

- accelerating enabling legislation;
- providing the supportive infrastructure and services, including seed supply and markets;
- generating well-trained and motivated scientists, for example with skills in plant breeding, crop protection and biosafety;
- informing and advising smallholder farmers in biotechnology stewardship for handling GM crops.

2. A. Kiggundu (National Agricultural Research Laboratories, Kawanda, Uganda), '*Current status of GM research and innovation in Uganda*'

Biotechnology is also regarded as one engine of economic transformation in Uganda. In participatory stakeholder discussions with farmers, it was clear that traditional breeding has limitations for improving locally preferred staple crops, many of which are vegetatively propagated, highly sterile, and where key desired traits are absent in the endogenous gene pools. The development of biotechnology goals for Uganda involved the following:

- identifying the problems where conventional breeding has not been successful;
- acquiring capacity in terms of infrastructure and skilled personnel;
- progressing technologies based on local crop varieties and biosafety research capacities (contained testing in greenhouse and confined field);
- testing for novel traits, in particular for banana resistance to bacterial wilt, the weevil borer, black sigatoka, and for micronutrient enhancement (beta-carotene and iron), and for cassava resistance to mosaic virus and brown streak virus (see later).

Other field trials are underway in Uganda on Bt cotton and water-use-efficient maize. Other R&D is targeting rice (nitrogen-use-efficient and salt-tolerant), sweet potato (disease resistance) and groundnut (disease resistance).

As elsewhere, the continuing challenges include the need to develop human resources capacity, create supportive policy and regulatory environments for innovation and commercialisation, ensure continuity in laboratory supplies and services and in research funding, and improve public awareness (hosting laboratory visits have been successful in this regard). Training programmes at national and regional levels are vitally important, including training for the regulatory bodies. International partnerships are also very important in sustaining R&D but such partnerships rarely now involve the EU.

3. R. Abdallah (Arusha, Tanzania), '*Preparedness of Tanzania to utilize genetically modified technology*'

Significant progress has been made in Tanzania in the routine application of techniques such as tissue culture and micropropagation, for banana and cashew, in marker-assisted breeding, and in developing skills in genomics and bioinformatics. Many GM applications can be envisaged to tackle biotic and abiotic challenges. The government has established the National Biosafety Framework that specifies the legal and institutional requirements for GMO applications but there is limited public understanding of the Framework and benefits of GM technology, which leads to uncertainty in decision making and adoption of the technology.

Many researchers consider that the Biosafety Regulation in Tanzania is too stringent. Only one GM project, on cassava, in a contained environment is currently taking place and this started before the Regulation was effected. A water-efficient maize project is next in the pipeline.

In discussing how to facilitate progress, the priorities for action were recommended to include the following:

- collective effort to increase public awareness of GM, to build understanding that may lead to acceptance and to encourage debate about which policies and regulations need to be formulated and what research needs to be supported;
- increased funding for R&D to build capacity;
- sustained support for regional and international cooperation;
- development of less stringent biosafety regulations, which may attract partners to work with scientists in Tanzania;
- more research on GM technology to enhance the decision-making process;
- responding to the challenge posed by activists from outside the country who misinform the public and create fears about the technology.

4. D.W. Miano (Kenya Agricultural Research Institute), '*Virus resistant cassava (VIRCA) project and issues arising*'

Cassava is a strategic crop for both food and income in Africa and it is the second most important food crop, after maize. Cassava productivity in Africa is lower than in South America and Asia and it is significantly constrained by two viral diseases: cassava brown streak disease and cassava mosaic disease. Challenges to disease management arise from the continuous presence of the virus, the attachment of farmers to particular cultivars which are susceptible and limited sources of resistance to the viruses. The Virus-Resistant Cassava for Africa (VIRCA) project was initiated to develop and deliver virus-resistant, farmer-preferred cultivars with desirable agronomic and storage quality attributes, using gene-silencing technology.

Scientific partnership between Kenya, Uganda and the USA provided a project management structure, constructed facilities, trained staff in the molecular techniques and in plant virology and biosafety compliance, data management and other necessary generic skills. Proof-of-concept for target cultivars has now been attained from an integrated programme of nine confined field trials to assess disease severity and virus incidence. A significant beneficial impact on agronomic performance has been observed in terms of disease severity. In the next phase, farmer-favoured cultivars will be used for transformation, efficacy testing and data collection to support regulatory approval and commercialisation. At the same time, the project is further engaging with stakeholders to communicate about the virus-resistant varieties, and planning for their dissemination to farmers in the region.

Discussion

Among cross-cutting issues emerging in wide-ranging discussion in the workshop were the following.

Capacity-building in critical areas is needed together with an enabling environment to secure the benefits from implementing a new technology. Capacity-building covers multiple dimensions, as follows.

- Regulatory capacity for sustainable technology development and up-scaling. Most countries have adopted, or in the process of doing so, some form of biosafety regulation: a useful basis for subsequent improvement.
- Communication capacity to inform farmers about the latest information so that they can make up their own minds about implementation, and to inform the public as potential consumers of

innovation. Many in the scientific community note that better information sharing is also needed to counter the unhelpful contribution by anti-GM activists, often coming from outside the African countries, who try to deter technology development (see also ASSAf, 2012).

- Human resources capacity and infrastructure for R&D. The EU is seen to have a valuable role in helping by training scientists and supporting research. Joint projects in laboratories in both continents will be welcome but, overall, the locus for collaboration would need to move from European to African institutions.

- Capacity for linking science and policy: to improve the interface and facilitate translation of advances in science and technology into practical applications. There is a key role for academies of science in providing independent, relevant and timely advice to inform policy options.

Creating and using the regulatory framework is of critical importance in harnessing technology, particularly in the early phases of technology development and implementation, before its impact can be fully ascertained. This is discussed in detail by ASSAf (2012) in their analysis of what proportionate biosafety regulation should cover. Whereas a relatively stringent and rigid approach to regulation might have been considered prudent early in technology development, a more flexible and proportionate approach can subsequently be entertained, based on accumulating scientific evidence and experience. Concern was expressed in the workshop that an excessively extended political debate about GM regulation discourages the scientific community. Thus, a relatively inflexible precautionary, approach to regulating biotechnology initially imported into African countries from the EU now merits reconsideration and reform. There will also be increasing opportunities for developing regional regulatory capacity and harmonising regulatory approaches in Africa.

Enhancing research infrastructure and filling research gaps is also vital to address African needs and opportunities. It was agreed that African countries should fulfil their promise to invest 1% of gross domestic product in science, technology and innovation and that agriculture is a major priority for this investment. The biosciences research agenda was discussed extensively in the workshop but, in addition, it was observed that more research is required in the social sciences in Africa to complement the biosciences and help to understand the social impact of innovation.

A new commitment to public-private partnership for R&D and innovation needs to build on the current situation where most research in agricultural biotechnology in Africa is within the public sector. Although multinational companies had initially been dominant in public–private partnerships worldwide, this is no longer the case. The Southern Agricultural Growth Corridor of Tanzania (SAGCOT, http://www.sagcot.com) initiated in 2010, provides an interesting risk sharing model of public–private partnership involving multiple stakeholders. Such models of partnership might also be more broadly relevant for developing the extension services, using expertise from NGOs or the private sector to deliver innovation.

The broader context of infrastructure for agricultural innovation must also be taken into account when considering how to benefit from genetic technologies. For example, without concomitant improvements in agronomic practices, organised food processing and marketing, any impact of a specific new technology will be diluted (ASSAf, 2012).

Labelling of GM products is a controversial topic and is scientifically indefensible for products that are substantially the same as those of non-GM origin. Currently, while GM products for export from Africa to the EU would have to be labelled, this would not necessarily be the case for local markets, and this dichotomy raises difficult issues for product segregation. There are cultural differences between African countries, as elsewhere, in attitudes to GM labelling. Further effort to raise awareness of the issues may be valuable as part of the discussion on setting coherent priorities for policy for African countries, for example in support of improved nutrition using GM biofortified crops.

Applying similar technologies elsewhere in the African bioeconomy also merits detailed consideration. There are various possible opportunities, for example, for bioremediation, and the production of energy, pharmaceuticals and other high-value chemicals from biomass. The workshop recommended that academies of science take a lead in informing and advising policy-makers to broaden their scope in understanding and enabling the potential applications of biotechnology and that the EU develop its partnership role with Africa in capacity building to address these other applications for the bioeconomy.

List of abbreviations

ATPS	Africa Technology Policy Studies
Bt	Genetically modified to express bacteria (*Bacillus thuringiensis*) toxin
CAP	Common Agricultural Policy
COST	European Cooperation in Science and Technology Framework
DG	Directorate-General (of the European Commission)
EASAC	European Academies Science Advisory Council
EFSA	European Food Safety Authority
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
GM	Genetically modified
GMO	Genetically modified organism
NASAC	Network of African Science Academies
NGO	Non-governmental organisation
PNT	Plant with a novel trait
R&D	Research and development

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Genome editing: scientific opportunities, public interests and policy options in the European Union

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Science Advice for the Benefit of Europe

EASAC

EASAC – the European Academies' Science Advisory Council – is formed by the national science academies of the EU Member States to enable them to collaborate with each other in giving advice to European policy-makers. It thus provides a means for the collective voice of European science to be heard. EASAC was founded in 2001 at the Royal Swedish Academy of Sciences.

Its mission reflects the view of academies that science is central to many aspects of modern life and that an appreciation of the scientific dimension is a pre-requisite to wise policy-making. This view already underpins the work of many academies at national level. With the growing importance of the European Union as an arena for policy, academies recognise that the scope of their advisory functions needs to extend beyond the national to cover also the European level. Here it is often the case that a trans-European grouping can be more effective than a body from a single country. The academies of Europe have therefore formed EASAC so that they can speak with a common voice with the goal of building science into policy at EU level.

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EASAC's activities include substantive studies of the scientific aspects of policy issues, reviews and advice about specific policy documents, workshops aimed at identifying current scientific thinking about major policy issues or at briefing policy-makers, and short, timely statements on topical subjects.

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European Academies

Science Advisory Council

Genome editing: scientific opportunities, public interests and policy options in the European Union

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Foreword

In many of the areas in which EASAC, the European Academies' Science Advisory Council, works, where a large and solid body of knowledge is needed to inform the action of our societies, it is important to recognise that there is an intimate mix of science and values involved in discussion. Such discussions are most fruitful when both knowledge and values are well identified. This report presents a broad synthesis of genome editing, one of the newer aspects of the biosciences. It is our hope that presenting clearly the science involved – the duty of academies – will serve the ongoing discussions within society that the report recommends be vigorously pursued.

Genome editing refers to the intentional modification of a targeted DNA sequence in a cell which, by greatly improving our understanding of biological functions, is beginning to revolutionise research.

This powerful new tool has significant potential for application in a wide range of sectors in pursuit of various societal priorities in human and animal health, food and agriculture, the modification of populations in the wild (in particular insect disease vectors) and microbial biotechnology and the bioeconomy. However, alongside the prospective benefits of the technology, safety, ethical and other issues have been raised that need to be explored, and regulatory questions posed that need to be addressed.

It is the purpose of this report from EASAC to take a broad perspective on the research advances and their potential applicability in different sectors to raise awareness of the opportunities and challenges, and to advise on the options to ensure an appropriate framework for managing innovation. It is our view that policy considerations should primarily concentrate on sector-specific product regulation and not on the general principles and practices of genome editing as a technology.

Our work covering the wide range of potential applications builds on previous activity by some of our EASAC member academies and on the ongoing work by our academy colleagues in FEAM, the Federation of European Academies of Medicine, who have focused on genome editing of human cells. Broadly, genome editing is a fast-moving area, not just in research and development but also in terms of the engagement between the scientific and policy communities.

Our report concentrates on recommendations for Europe, but the issues are of great global interest. For example, after our report drafting was complete, the US National Academies of Sciences, Engineering, and Medicine published their final report on the science, ethics and governance of human genome editing[1]. These very recent US recommendations on basic laboratory research and human somatic genome editing are substantially similar to the interim conclusions from the international summit that are discussed in our report. However, the latest US conclusions about human germline (heritable) genome editing extend the potential scope in that they note the possibility of identifying circumstances in which clinical research trials would be permissible for germline genome editing. These circumstances are posited to include a compelling clinical purpose and stringent oversight system. Such recommendations are controversial[2], not least in some of our European Union (EU) Member States, and will require considerable further public engagement by the scientific and medical communities to debate issues and perspectives.

It is not only human genome editing that attracts controversy. Recently, the EU Scientific Advice Mechanism – the newly constituted process to provide the European Commission with high-quality, timely and independent scientific advice on specific policy issues – has started an inquiry[3] on 'New techniques in agricultural biotechnology', and we welcomed the opportunity to contribute our pre-publication findings to this initiative.

This report has been prepared by consultation with a group of experts nominated by our member academies. I thank them and their chairman, Professor Volker ter Meulen, and the EASAC Biosciences Programme Director, Dr Robin Fears, for their expertise, insight and enthusiasm in assessing a wide range of issues and in achieving consensus in the conclusions and recommendations. I also thank our colleagues in FEAM, our independent peer reviewers, our EASAC Biosciences Steering Panel for their guidance, and EASAC council members and their academies for continuing assistance in communicating our messages at the national level as well as to EU institutions.

We believe that our findings are relevant to a wide spectrum of EU and national policy-making. EASAC

[1] The National Academies of Sciences, Engineering, and Medicine 'Human Genome Editing: Science, Ethics and Governance', https://www.nap-edu/download/24623#.
[2] For example, www.sciencemediacentre.org/expert-reaction-to-the-publication-of-new-report-on-gene-editing.
[3] http://ec.europa.eu/research/sam/index.cfm?pg=agribiotechnology.

stands ready to continue contributing to the active debates on contentious points for research and innovation, and on other relevant matters, for example the global implications for biosecurity. Because genome editing is a fast-moving area in many respects, we will be willing to return to our exploration of the topics in this report in due course. To inform our further thinking, we now welcome discussion of any of the points that are raised in our report, or indeed any others that require attention.

Thierry J-L Courvoisier
EASAC President

Summary

Genome editing, the deliberate alteration of a selected DNA sequence in a cell, using site-specific DNA nuclease enzymes, has become a very important tool in basic research. Genome editing has been described by some as a transformative technology and, certainly, in some areas of research and innovation, it is transforming expectations and ambitions. Genome editing can specifically modify individual nucleotides in the genome of living cells and, together with a growing ability to monitor and reduce off-target effects, it brings new opportunities within range. Because of its general applicability (in microbes, and plant, animal and human cells) it has a very wide range of potential uses in tackling societal objectives. These potential applications include, but are not limited to, gene- and cell-based therapies to control diseases and, in reproduction, approaches to avoid the inheritance of disease traits; the control of vector-borne diseases; improved crop and livestock breeding, including improved animal welfare; modification of animal donors for xenotransplantation; and industrial microbial biotechnology to generate biofuels, pharmaceuticals and other high-value chemicals.

The advent of genome editing has evoked enthusiasm but also controversy. Concerns have been expressed, by some non-governmental organisations (NGOs) for example, that genome editing is 'not natural', that there are too many gaps in our knowledge, that impacts are uncertain and may be inequitable, and that regulation cannot keep pace with the speed of technological innovation.

In this report, EASAC takes a broad perspective on the research advances in editing methods and their applications, policy implications and priorities for EU strategy in promoting innovation and managing regulation. Our report draws on previous work by individual academies in Europe and by other international academy collaborations. Our objectives are to raise awareness of the scientific opportunities and public interest issues: to assess what needs to be done to realise those opportunities and take account of societal concerns.

Current knowledge gaps and uncertainties emphasise the need for more basic research. We expect that research advances will fill many of the current knowledge gaps and that progressive refinement of genome editing tools will further increase their efficiency and specificity, thereby reducing off-target effects. We anticipate that the fast pace of change in research and innovation will continue, so EASAC is willing to return to the subject of this report in due course to review its assessments.

EASAC concludes that policy considerations should focus on the applications in prospect rather than the genome editing procedure itself as an emerging technology. It is important to ensure that regulation of applications is evidence-based, takes into account likely benefits as well as hypothetical risks, and is proportionate and sufficiently flexible to cope with future advances in the science. Our recommendations are as follows.

Plants

The increasing precision now possible in plant breeding represents a big change from conventional breeding approaches relying on random, uncontrolled chemical- or radiation-induced mutagenesis and meiotic recombination. In supporting the conclusions from previous EASAC work on new plant breeding techniques, we recommend the following.

- We ask that EU regulators confirm that the products of genome editing, when they do not contain DNA from an unrelated organism, do not fall within the scope of legislation on genetically modified organisms (GMOs).

- We advise that there should be full transparency in disclosing the process used, but that the aim in the EU should be to regulate the specific agricultural trait/product rather than the technology by which it is produced. It follows that new technologies would be excluded from regulation if the genetic changes they produce are similar to, or indistinguishable from, the product of conventional breeding and if no novel, product-based risk is identified.

Animals

Research on animals is already subject to stringent regulation. While most genome-edited animals are currently being generated for basic or biomedical research, the technology also provides opportunities for livestock and aquaculture. It should be appreciated that, in addition to potential increases in production, genome editing brings possibilities to enhance animal health and welfare. For specific applications, we recommend the following:

- Livestock breeding in agriculture should also be governed by the same principle as proposed for plant breeding—to regulate the trait rather than the technology and be open and explicit about what is being done.

- With regard to the modification of large animals to serve as a source for xenotransplantation, we urge EU regulators to prepare for the new opportunities coming into range: this may require further discussion of the mechanism for approving medical products relating to cells and tissues, together with assessment of the implications of whether the edited donor, in the absence of additional transgenes, is regarded as a GMO or not.

Gene drive to modify populations in the wild

Gene drive applications for vector control and other modifications of target populations in the wild offer significant potential opportunities to help address major public health and conservation challenges. As outlined recently by the US National Academies of Sciences, Engineering, and Medicine, a phased approach to research can enable responsible development and offers sufficient time for considering what amendments are needed to current regulatory frameworks to enable the sound evaluation of a gene-drive-based technology. EASAC supports the recommendations by the US National Academies on gene drive approaches:

- It is essential to continue the commitment to phased research to assess the efficacy and safety of gene drives before it can be decided whether they will be suitable for use.

- This research must include robust risk assessment and public engagement.

- EU researchers must continue to engage with researchers and stakeholders in the countries where gene drive systems are most likely to be applied.

Micro-organisms

- We conclude that genome editing in microbes does not raise new issues for regulatory frameworks and is currently subject to the established rules for contained use and deliberate release of GMOs.

- There is a wide range of potential applications, including pharmaceuticals and other high-value chemicals, biofuels, biosensors, bioremediation and the food chain. It is important to recognise this wide range when developing EU strategy for innovation in the bioeconomy.

- Many of the policy issues for microbial genome editing research and innovation fall within the scope of what is regarded as synthetic biology, and we reaffirm the general recommendations from previous EASAC work relating to building research capacity, promoting skills development and recognising the need to achieve a balance between protection of innovation and benefit-sharing.

- Concerns have been raised elsewhere about the possibility for genome editing research to be conducted outside regulated laboratory settings. We recommend that the Global Young Academy should assess the issues raised by the expansion of the Do-It-Yourself (DIY) biology community.

- Concerns have also been expressed elsewhere about the potential biosecurity implications of genome editing. We recommend that the scientific community continues to inform and advise policy-makers during review of the Biological and Toxin Weapon Convention.

Human-cell genome editing

EASAC endorses the emerging conclusions from other collective academy work (International Summit on Gene Editing and FEAM) and the initiatives of EASAC member academies:

- *Basic and clinical research.* Intensive research is needed and should proceed subject to appropriate legal and ethical rules and standardised practices. If, in the process of research, early human embryos or germline cells undergo genome editing, the modified cells should not be used to establish a pregnancy. EASAC recognises that the decision by the European Commission not to fund research on embryos will be unlikely to change at present.

- *Clinical use: somatic gene editing.* There is need to understand the risks such as inaccurate editing and the potential benefit of each proposed genome modification. These applications can and should be rigorously evaluated within existing and evolving regulatory frameworks for gene and cell therapy by the European Medicines Agency and national agencies.

- *Clinical use: germline interventions.* These applications pose many important issues including the risks of inaccurate or incomplete editing, the difficulty of predicting harmful effects, the obligation to consider both the individual and future generations who will carry the genetic alterations, and the possibility that biological enhancements beyond prevention and treatment of disease could exacerbate social inequities or be used coercively. It would be irresponsible to proceed unless and until

the relevant ethical, safety and efficacy issues have been resolved and there is broad societal consensus.

General recommendations for cross-cutting issues

- *Public engagement.* There has to be trust between scientists and the public and, to build trust, there has to be public engagement. Stakeholders, including patients, clinicians, farmers, consumers and NGOs, need to be involved in discussions about risk and benefit, and scientists need to articulate the objectives for their research, potential benefits and risk management practices adopted. There is need for additional social sciences and humanities research to improve public engagement strategies.

- *Enhancing global justice.* There may be risk of increasing inequity and tension between those who have access to the benefits of genome editing applications and those who do not, although the widespread adoption of the technique might facilitate the sharing of benefits. The scientific community must work with others on the determinants to narrow the societal gap: for example, by active knowledge transfer, collaboration between researchers worldwide, open access to tools and education, and education efforts. It is also vital for EU policy-makers to appreciate the consequences, sometimes inadvertent, of EU policy decisions on those outside the EU. There is evidence that previous decisions in the EU (for example, on GMOs) have created difficulties for scientists, farmers and politicians in developing countries. Reforming current regulatory frameworks in the EU and creating the necessary coherence between EU domestic objectives and a development agenda on the basis of partnership and innovation are important for developing countries as well as for Europe.

1 Introduction

Genome editing is the alteration of a targeted DNA sequence, achieved by cutting the DNA molecule at a selected point, which activates the cell's own repair system and thus results in small deletions or insertions[4]. This is commonly used to inactivate a target gene or target sequence. When, at the same time, exogenous DNA is introduced, this can support the repair at the target site and enable a predetermined exchange of single or multiple nucleotides (targeted mutagenesis), for example to replicate or rectify a naturally occurring mutation. In this eventuality, the genome-edited organism would be indistinguishable in this specific place of the genome from an organism in which the mutation occurred naturally. The same method can also be used to insert or exchange fragments of foreign DNA at a predetermined site in the genome, generally then resulting in an organism carrying a transgene.

In this report, EASAC takes a broad perspective on the research advances, applications, policy implications and priorities for EU strategy in promoting innovation and managing regulation. The issues reviewed in our report are relevant for policy-makers at the EU level as well as in Member States: we emphasise the importance of developing consistency and coherence in the principles underpinning policy across the EU, with compatibility between different sectors, in support of research and its translation to innovation.

1.1 What are the prospects for genome editing?

Genome editing to produce selected disruption, correction or integration of genetic material in a cell has significant potential in basic research – including the elucidation of currently poorly understood biological functions of genetic elements – and in wide-ranging fields of application. Genome editing differs from previously employed techniques of genetic engineering in that alterations can be introduced more efficiently and precisely at the molecular level. However, there is more to be done in many cases to understand the biological consequences of those nucleotide changes. Genome editing is a significant scientific advance which, at the same time, may accentuate ethical and social questions associated with some potential applications coming within reach.

The science is advancing rapidly but the technology is already sufficiently mature to warrant assessment of the opportunities and of the challenges for ensuring proportionate, robust and flexible management of research and innovation. There are relevant matters for several EU policy-making departments, relating to the regulation of new products and the avoidance of harm, whether harm is caused inadvertently to human health and the environment, or by intended misuse, with biosecurity consequences.

There are significant strengths in European research in genome editing and it is important that rigorous risk–benefit assessment is part of the regulatory process, that any safety concerns are addressed and that research outputs can be translated into new products and services to fulfil societal needs, underpin the EU bioeconomy[5] and support European competitiveness. Potential benefits include the following: microbial biotechnology, for example in the provision of more efficient pathways for biofuel synthesis, high-value chemicals and pharmaceuticals; new vehicles for drug delivery; sensors and environmental remediation; plant and animal breeding in precision agriculture to tackle issues of food and nutrition security, animal health and a more sustainable agriculture; and a range of other human health applications (Hsu *et al.* 2014; Carroll and Charo, 2015; Barrangou and Doudna, 2016). Tackling disease, genome editing of human cells brings opportunities to treat or avoid monogenic disorders (with recent research in cystic fibrosis, Duchenne muscular dystrophy, diseases affecting the immune system and haemophilia (Prakash *et al*., 2016)) and infectious disease (with first studies in human immunodeficiency virus (HIV)) and diseases that have both a genetic and an environmental component (Porteus, 2015). Examples of prospective benefit and of perceived risks will be discussed later in this report.

1.2 Definition and experimental procedures

Genome editing refers to DNA mutations that are targeted to a specific region of the genome by site-specific nucleases (SSNs). It does not exclude the possibility that mutations in other regions of the

[4] Further scientific detail and the potential for alternative approaches to genome editing are provided in Box 1.

[5] The bioeconomy is regarded strategically as a key component for sustainable growth in the EU (European Commission, 2012). The economic value of genome editing is difficult to forecast and depends, of course, on its eventual contribution to the different fields of application in the bioeconomy (and the share that the EU can appropriate). Currently, the EU's biology-based industries account for 8.5% of the region's work-force, with an annual turnover of more than €2 trillion (El-Chichakli *et al*., 2016). According to the Organisation for Economic Co-operation and Development (OECD), the worldwide export of products related to the bioeconomy in 2014 amounted to about 13% of world trade. Recent comprehensive analysis of the biotechnology sector's contribution to the US economy indicates it is currently about 2% of US gross domestic product (within this 2%, approximately similar proportions are contributed by biotechnology medicines, crops/seeds and industrial products such as biofuels, enzymes and biomaterials (Carlson, 2016)).

genome also occur during the genome editing process: to avoid these unintended consequences, tools are being sharpened to prevent off-target effects.

Two forms of mutagenesis need to be distinguished:

- Simple mutagenesis (non-homologous end-joining), resulting either in base-pair substitutions or small insertions or deletions. This form is indistinguishable from spontaneous or induced random mutagenesis.

- Homologous recombination, in which a template of DNA is supplied with the SSN enabling the replacement of a similar sequence in the genome, or insertion of the added DNA in the genome at a pre-specified place. This form is similar to transfer of genetic material from one species to another after conventional crosses, or in cases of a more distantly related donor of the template DNA, similar to naturally occurring lateral/horizontal gene transfer.

A separate consideration is whether genome editing is achieved by insertion of DNA sequences that code for the editing agent (for example, CRISPR–Cas9) into the genome (and later removed by genetic segregation) or whether the editing agent is introduced transiently as DNA, RNA and/or protein without any integration of foreign DNA sequences into the cell.

Further scientific detail about the recent history of genome editing is provided in Box 1.

1.3 Public interests and values

The outputs from genome editing may have direct or indirect impacts on the well-being and welfare of the public—and the advent of genome editing evokes not only enthusiasm but also controversy. As will be discussed later in this report, when public concerns are elicited, they are usually about the intended use rather than the technology itself. Various queries have been raised about the different applications of genome editing, reflecting field-specific drivers and obstacles, but there are also generic questions that can be asked, as observed in the consultation for the UK Nuffield Council on Bioethics inquiry on genome editing (2015). For example, to what extent can the development of new genome engineering techniques be regarded as distinct from, or continuous with, existing techniques? Does the ease and accuracy of genome editing mean that it is a transformative technology (in either the moral or economic senses) and, therefore, represents a 'tipping point' in the potential of genetic engineering? Should a distinction be made (as it is by some who query these techniques) between directed change and those undirected changes induced, for example, by chemical- or radiation-induced mutagenesis, in conventional plant breeding programmes? There is also a generic technical point that is relevant to the various fields of application. Editing makes only small changes to DNA. At the target site these are easily identified, but off-target changes, which also occur in random mutagenesis, may be difficult to detect without full DNA sequencing. What implications does this have for the regulation of the resulting product?

Potential problems for assessing the products of this emerging technology are compounded in the EU by a legacy of contention and polarisation about the regulation of genetic engineering techniques. Current EU legislative frameworks governing the genetic modification of plants and animals, for example, are controversial; and even when there is an overarching EU policy framework, there is little certainty for researchers and breeders, because individual Member States vary in their implementation or can exercise an 'opt-out'. As critically observed by a recent Member State parliamentary report (UK House of Commons Science and Technology Committee, 2016), '*The regulation of genetic science is an area in which the EU has so far not come close to satisfactorily demonstrating an evidence-based approach to policy making*'.

Responsible innovation requires attending to ethical, legal and societal issues, and seeking to identify common goals important to scientists and the public. Researchers and their funders have a responsibility to engage with the public and to take account of public interests and values. In genome editing these range from the protection of individuals or populations from possible health risks, protection of animals from risks to their health and welfare, to moral and political interests around the acceptable limits to intervening in natural processes (Nuffield Council on Bioethics, 2015).

There is a moral obligation to fight disease and relieve humans and animals from suffering. To the extent that genome editing technologies provide useful tools to achieve such purposes, there is an opportunity cost in using them too late or not at all, particularly if they are safer, more effective and cheaper than alternative technologies. Concerns have been expressed about whether regulation can keep pace with the speed of technological innovation, whether scientists (and society) have fully appreciated the implications of what science can deliver and whether it would be possible to reverse undesirable outcomes. Much of the public debate has focused on human germline modification (which means that genetic changes would be heritable), but ethical issues relating to views of nature and ecosystems are also relevant to applications encompassing non-human targets of genome editing (Charo and Greely, 2015).

Application-specific issues are discussed in our subsequent chapters. General concerns expressed,

Box 1 Summary of the science of programmable nucleases

Genome editing methods take advantage of exogenous programmable nucleases to make double-stranded DNA breaks at selected sites. These breaks activate endogenous repair mechanisms either non-homologous end-joining (NHEJ) or homology-directed repair (HDR). The latter operates when a DNA donor template is provided, and both systems function in all eukaryotic organisms. NHEJ is a more prevalent, error-prone mechanism that often causes mutations (short insertions or deletions), resulting in target gene knockout, when the break is introduced in the coding sequence of a locus; whereas HDR, which functions only in the synthesis (S) and gap 2 (G2) phases of the cell cycle, is the way to knock-in or substitute a desired sequence, for example to replace a mutant DNA fragment for the normal one. The NHEJ efficiency at the site of induced double-stranded DNA break is usually about five- to eight-fold higher than the efficiency of HDR.

The first generation of gene editing tools was based on oligonucleotide-directed mutagenesis (ODM) or microbial meganucleases, possessing long DNA recognition sequences. They were cumbersome to use and often suffered from low efficiency, especially ODM. The desired flexibility in target sequence recognition was achieved with the use of engineered zinc finger nucleases (ZFNs: each finger recognises about three specific nucleotides of DNA) and more recently with transcription activator-like effector nucleases (TALENs: each TALEN recognises short double-stranded specific sequence, typically single nucleotides). In both ZFN (Kim *et al.* 1996) and TALEN (Cermak *et al*., 2011) designs, the DNA recognition module is additionally coupled via a peptide linker to an unspecific DNA cleaving portion, usually the Fok I restriction nuclease domain. As only dimerised Fok I shows DNA cleavage activity, the length of the DNA recognising portion is also doubled by involving two recognition arms, enhancing nuclease specificity. Although TALENs had several advantages over ZFNs, especially in their design, their production is still a laborious process.

Another class of genome editing tool is designer recombinases. Similar to meganucleases, recombinases are difficult to tailor and the generation of enzymes with new DNA-binding specificities is cumbersome and time consuming. However, designer recombinases are highly specific and do not rely on cellular DNA repair as they cut and re-ligate the DNA in a conservative manner. As such, designer recombinases represent interesting alternatives (Karpinski *et al*., 2016), subject to further research.

The revolution in the field of genome editing came in 2012 with the development of the CRISPR–Cas9 system (Jinek *et al*., 2012), which is much easier to design, produce and use. The acronym CRISPR stands for clustered regularly interspersed short palindromic repeats, and it is considered by some to be a distant bacterial analogue of the RNA interference mechanism in eukaryotes; Cas stands for CRISPR-associated protein nuclease. The system is based on the natural defence mechanism against bacteriophages and plasmids evolved by many bacteria and archaea. Unlike protein meganucleases, ZFNs and TALENs, the new system uses RNA for complementary DNA recognition, and Cas9 protein (or related protein) to recognise a matching target sequence in the DNA, flanked by a short protospacer adjacent motif (PAM), and execute DNA cleavage by its two DNase domains. The RNA component is either composed of two molecules, the CRISPR RNA (crRNA) and trans-activating crRNA (tracrRNA) as in the bacteria it derives from, or, what is more common, these two RNAs are fused by researchers into a single guide RNA (gRNA) which is about 100 nucleotides long.

How does the CRISPR–Cas9 system function? In brief, the Cas9 protein is bound to a gRNA and thereby programmed to recognise a target DNA whose sequence is complementary to a ~20 nucleotide segment in the gRNA. Cas9 binds the PAM motif in the target DNA duplex, separates the DNA strands and facilitates base-pairing between the gRNA and the complementary DNA sequence. Subsequently, Cas9 deploys its two DNase domains, RuvC and HNH, to cleave target DNA, generating a double-stranded break. Then, the DNA repair systems, NHEJ or HDR come into action and DNA is either mutated or replaced. The editing process with CRISPR–Cas9 may be multiplexed to inactivate tens of targets at once (Yang *et al*., 2015).

The important practical issues in genome editing experiments are the delivery of programmable nucleases into cells, their cleavage efficiency and specificity, in terms of avoiding off-target effects. To minimise the off-target effects, new versions of Cas9 and related proteins have been engineered. Recently, a mutation of three or four amino acids in the Cas9 catalytic domain reduced off-target effects dramatically to levels that were hardly noticeable (Klenstiver *et al*., 2016). Furthermore, in addition to Cas9, other bacterial DNases such as Cpf1 (Zetsche *et al*., 2015), which recognise different PAM sequences, can also be used for genome editing and thus increase the range of targetable sequences in genomes.

Besides genome editing, the CRISPR–Cas9 system has been repurposed for sequence-specific regulation of gene expression, either transcription activation or repression, or specific gene imaging using nuclease-deactivated Cas9 termed dCas9 (Dominguez *et al*., 2015). The CRISPR–Cas9 system has also been adapted to recognise and track RNA in living cells (Nelles *et al*., 2016), and a natural RNA-targeting CRISPR system taking advantage of the C2c2 enzyme has been identified (Abudayyeh *et al*., 2016).

for example by some NGOs, that genome editing is not natural, and that there are too many gaps in our knowledge and that impacts are uncertain, as well as there being issues for global justice[6], can probably be applied to all emerging technologies in biology and medicine. It is the role of research and of robust regulatory systems to continue to address the uncertainties and fill the knowledge gaps in a transparent way. A cardinal feature of the accuracy of genome editing is that the functional consequences should be more predictable than when using earlier techniques. Of course, there is continuing need to adopt appropriate safety standards, develop risk assessment techniques and to install effective surveillance, monitoring and disclosure systems, whatever the field of application. The recent report from the Nuffield Council on Bioethics (2016) considers further the range of ethical questions to which the recent advances in

[6] That is, would the societal gap increase between those who are able to use the technologies for their own benefit in medical, agricultural or other applications, and those who are not?

genome editing may give rise. These issues and the implications of the 'slippery slope' argument will be dealt with at various places in our report.

Public interest about science and innovation also often refers to the desirability of open science, benefit-sharing and fair competition. There is controversy about competing patent claims for CRISPR–Cas technology (Egelie *et al.* 2016; Nuffield Council on Bioethics, 2016). At the same time, CRISPR–Cas9 has become an example of open science, where the development of the procedures has resulted in the sharing of tools from more than 80 laboratories.[7] Patent-related aspects were addressed in a recent statement from ALLEA, the All European Academies (2016) which notes that the use of CRISPR–Cas technology does not require any reforms in patent law: '*EU patent law provides the necessary incentives for further development and use across all fields of life sciences*' and that there will be no patents granted which could offend human dignity and/or integrity.

1.4 Previous work by academies of science and medicine

There has already been a significant amount of work by academies on the issues elicited by genome editing and our EASAC report draws on this continuing effort:

- *At the national level in Europe,* the German Academies statement (Leopoldina *et al*., 2015) on opportunities and limits, covers all applications and emphasises the great scientific potential of genome editing in opening up new scope for basic research. This German statement concludes that it is ethically and legally acceptable in many areas (see Chapter 5 of the present report for further discussion, including a moratorium of genome editing for germline interventions[8]) and that new techniques should not automatically be equated with sporadic cases of improper use or with applications whose ethical and legal ramifications have not yet been assessed. While our EASAC study was in progress, KNAW, the Royal Netherlands Academy of Arts and Sciences (2016), published their national position paper on genome editing. This also covers multiple applications and their recommendations are broadly consistent with the recommendations in the present EASAC report.

- *The International Summit on Human Gene Editing* is led by the US National Academies of Sciences, Engineering and Medicine together with the UK Royal Society and the Chinese Academy of Sciences. This consortium is examining the scientific underpinning as well as the clinical, ethical, legal and social implications of the use of human genome editing technologies in biomedical research and medicine, including editing of the human germline (National Academies, 2016a).

- *The US National Academies* have also completed investigations of genome editing and gene drive (National Academies, 2016b), and of genome editing relevant to laboratory animal use.

- *FEAM* organised a workshop in 2016; with support from the InterAcademy Partnership (IAP), to consider the landscape for human genome editing in the EU. This workshop reviewed current scientific and regulatory activity in human genome editing research and clinical applications, to identify where there are significant differences between EU countries and to discuss options for European-level activities (Academy of Medical Sciences, 2016). The report from this workshop was recently published (FEAM, 2017).

The outputs from these other academy activities will be cross-referenced in the following chapters of our report.

1.5 EASAC objectives for this work

In seeking to add value to the work that has already been done, this report draws on the previous academy publications together with advice and information from a group of experts nominated by EASAC member academies (Appendix 1). We take a broad perspective of the science, and our objectives for this report are also wide-ranging in assessing policy and practice:

- To raise awareness across Europe of the scientific opportunities of the new genome editing techniques, and public interest issues, to evaluate what is now needed to realise those opportunities and address those issues, and to consider who should make decisions on governance.

- To identify distinctive aspects confined to particular applications of genome editing, to show where sector-specific outputs are already subject to established policies rules and regulations (at institutional, national and

[7] www.addgene.org/crispr

[8] In Germany, germline therapy and the use of modified germ cells for fertilisation are prohibited under Section 5 of the German Embryo Protection Act. Whether the intervention would be allowed if it served the preservation of the resulting embryo is under debate. The German academies have also published a Statement on progress in molecular breeding and on the possible national ban on cultivation of genetically modified (GM) plants: see https://www.leopoldina.org/uploads/tx_leopublication/2015_03_26_Statement_on_Molecular_Breeding_final.pdf

EU levels) or where changes should now be foreseen.

- To prepare policy-makers to address those issues that have still to be clarified and resolved.

- To serve as an input to global discussions and action on genome editing priorities, alongside the other academy initiatives (that focus on human-cell applications) and for those aspects where global consensus is of particular importance (for example, for biosecurity).

As part of these objectives, we aim to assess what strategic objectives are relevant to the EU level and what is reserved for Member States. EASAC messages are directed to those who make or influence policy in EU institutions, and at Member State level, academies of science in other regions outside the EU, research funding bodies, regulatory authorities, professional societies and others in the scientific community. We recognise the great importance of also engaging with other stakeholders and the community-at-large, and EASAC encourages its member academies to use this report as a resource to disseminate our messages widely.

In the following chapters, we consider particular applications of genome editing and in the final chapter bring together our conclusions and recommendations.

2 Plants and animals

For both plants and animals, genome editing has become an essential tool for basic research, to elucidate gene function and to generate model plants and animals. The scientific advances achieved with genome editing, capitalising also on the progress in genome sequencing that is identifying many genes and alleles of interest for agriculture, enhance the potential for tackling a wide range of applications.

There are major global challenges to be faced in addressing issues for food and nutrition security and agriculture, and the opportunities and challenges are discussed more broadly in an ongoing EASAC project that constitutes the European arm of a worldwide IAP project[9]. Current problems of food and nutrition security are compounded by pressures of growing population, climate and other environmental changes, and by economic inequity and insecurity. Setting priorities for increasing agricultural production must also take account of pressures on other critical resources, particularly water, soil and energy, and the continuing imperative to avoid further loss of ecosystems and biodiversity.

2.1 Plant breeding in agriculture

Plant sciences can do much in continuing to contribute to increased crop quality, for example in developing cultivars with improved water and nitrogen use, better resistance to pests and diseases, or modified crop architecture to reduce waste. Prospects for plant genome editing are discussed widely in the literature (see, for example, Bortesi *et al*., 2016; Quetier, 2016) and in the recent report from the US National Academies (2016c) which notes the potential of genome editing to introduce more complex changes because multiple genes can be edited simultaneously. Genome editing brings new possibilities to improve plant traits, beyond what has been achieved with the previous generation of genetic modification (mutagenesis) approaches. Molecular targets are being selected and tackled to increase yield, stress- and disease-resistance, elevate nutrient use efficiency and reduce allergens, for example, in broad support of the societal objectives for increased food production, conservation of natural resources, less pollution and healthier food. There are many significant research advances described in the US National Academies report and in other recent publications, for example the induction of targeted heritable mutations in barley and brassica (Lawrensen *et al*., 2015) and combatting invading virus DNA in plants (Zhang *et al*., 2015). Of particular interest in breeding is the rapid introduction of known natural alleles (genetic variation) into many different genetic backgrounds.

Research advances in plant breeding are now being translated into novel products. There has been recent progress using genome editing in the commercial development of cold-storable potatoes and no-trans-fat soybean oil, but the first organisms to be allowed by the US Government are CRISPR–Cas9-edited mushrooms (with reduced browning by reducing the activity of the endogenous enzyme polyphenol oxidase) and a waxy corn engineered to contain starch composed exclusively of the branched polysaccharide amylopectin (used in processed foods, adhesives and high-gloss paper). These products do not come within US Department of Agriculture regulations (Waltz, 2016) although they might still be submitted for voluntary review by the US Food and Drug Administration (FDA).

These rapid advances in research and development accentuate a major underlying question for the EU: to what extent will the regulation of plants/food products developed using genome editing be influenced by previous controversies and current legislation on GMOs? The products of genome editing may contain no foreign DNA, and EASAC has previously advised in the Statement on New Breeding Techniques (2015a; encompassing genome editing tools and summarised in

Box 2 Summary of previous EASAC recommendations on new plant breeding techniques

1. EU policy development for agricultural innovation should be transparent, proportionate and fully informed by the advancing scientific evidence and experience worldwide.
2. It is timely to resolve current legislative uncertainties. We ask that EU regulators confirm that the products of new breeding techniques, when they do not contain foreign DNA, do not fall within the scope of GMO legislation.
3. The aim in the EU should be to regulate the specific agricultural trait and/or product, not the technology by which it was produced.
4. The European Commission and Member States should do more to support fundamental research in plant sciences and protect the testing in field trials of novel crop variants against vandalism.
5. Modernising EU regulatory frameworks would help to address the implications of current policy disconnects in support of science and innovation at regional and global levels. At the same time, there is continuing need for wide-ranging engagement on critical issues and this should include re-examination of the appropriate use of the precautionary principle.

Source: EASAC (2015a)

[9] 'Food and nutrition security and agriculture', see www.interacademies.net/News/27419.

Box 2) that such processes should not be regulated in the same way as GMOs, assuming that there is evidence to demonstrate that any transgene has been segregated away in the final product.

The issues are, however, still contentious. For example, if there is a transient transgenic stage during the plant breeding process, some would assert that this makes the final non-transgenic product still a GMO. However, modern whole-genome sequencing methods allow for unambiguous proof that foreign DNA from transgenes has been completely removed. It should also be noted that many of the agricultural sector-specific public concerns raised by NGOs about genome editing were also raised previously in the early days of genetically modified (GM) crops[10] and were addressed systematically then (for example in the UK GM science review (GM Science Review Panel 2003), and see EASAC (2013) for further discussion of the GM crop research evidence base).

A European Commission decision on the status of these products is urgent in view of the accelerating pace of research and development and of the regulatory initiatives being undertaken by individual Member States. For example, an oligonucleotide gene-edited canola strain was assessed as non-GMO in Germany (EASAC 2015a; Huang *et al*., 2016; and see the footnote[11]). The Swedish Board of Agriculture, a national competent authority, also confirmed that some plants in which the genome had been edited using CRISPR–Cas9 do not fall under the EU GMO definition[12]. Discussion in the EASAC Working Group agreed that a strong case can be made for genome-edited crops to be subject only to the rules and regulations that apply to products of conventional breeding, subject to certain guiding principles (Huang *et al*., 2016):

- Minimising the risk of escape of genome-edited crops from laboratories and fields during the research and development (R&D) phase.
- Demonstrating the absence of foreign sequences if genome engineering proteins were introduced as DNA constructs.
- Documenting DNA sequence changes at the target sites.
- In the case of newly introduced DNA, identifying the phylogenetic relationship between donor and recipient.
- Excluding unintended secondary editing events or off-target sites on the basis of available reference genome information.

Even if a trait-based assessment system did not require specific regulation of a new crop variety, there should still be a legal requirement to disclose the process used, with transparency on why a particular process was used. The alternative regulatory options for genome-edited plants, including product-based approaches, are discussed further in detail by Sprink *et al.* (2016).

Recommendations from the European Commission on what is a GMO are delayed, and continuing discussion with the European Commission, European Parliament and Council of Ministers is expected. There is great need for evidence-based proportionate regulation for next-generation plant breeding (Box 2). EU regulatory frameworks should also take account of best practice outside the EU (EASAC 2013, 2015a). For example, reform of the US system for regulation of GMOs and of products using other techniques such as genome editing, which do not currently fall within US GMO regulations, is anticipated in the new US Coordinated Framework for regulating biotechnology. It has been proposed (Strauss and Sax, 2016) that this new US Framework should be product-based not event-based; novelty-based not method-based; and that modifications that are analogous to what occurs in conventional breeding (but which are more precise and better understood than in conventional breeding) should be exempt, unless a novel product-based risk is identified. It would seem reasonable to consider adopting similar criteria in the EU (and compatible with the recommendations in Box 2), while also taking into account essential features of the responsible governance of agricultural biotechnology (Hartley *et al*., 2016), including a commitment to candour, recognition of underlying values and assumptions, and a preparedness to respond to new knowledge or concerns.

Recent proposals from the US Government give some indications of how the revised US regulatory system might function. The US Department of Agriculture's Animal and Plant Health Inspection Service (APHIS, 2017) set out the criteria by which an organism would not be regarded as genetically engineered. For example, it would not be regarded as a genetically engineered organism if the modification were solely a deletion of any size or a single base-pair substitution that could otherwise be obtained through the use of chemical- or radiation-based mutagenesis. It would also not be

[10] These concerns included potential for human toxicity, allergenicity and effects on the environment.
[11] The German Federal Office of Consumer Protection and Food Safety provided an Opinion on the legal classification of New Plant Breeding Techniques, including CRISPR–Cas9, see https://www.bvl.bund.de/SharedDocs/Downloads/06_Gentechnik/Opinion_on_the_legal_classification_of_New_Plant_Breeding_Techniques.pdf?_blob=publicationFile&v=2.
[12] November 2015 'Green light in the tunnel!', Umea Plant Science Centre www.upsc.se.

considered a genetically engineered organism if the modification were solely introducing only naturally occurring nucleic acid sequences from a sexually compatible relative that could otherwise cross with the recipient organism and produce viable progeny through traditional breeding (including, but not limited to, marker-assisted breeding, as well as tissue culture and protoplast, cell or embryo fusion). As part of its broader initiative in biotechnology (see subsequently for issues raised for animals and mosquitoes), the FDA has also very recently invited comments on whether genome-edited plants might present new food safety risks and whether they should follow the same pre-market regulatory review at the FDA as transgenic plants currently do[13]. An accompanying commentary[14] emphasises the FDA principle to maintain product-specific, risk-based regulation.

A second international example is provided by Australia, currently conducting a review and public consultation to provide clarity on whether organisms developed using a range of new technologies (including site-directed nuclease techniques) are subject to regulation as GMOs and to ensure that new technologies are regulated in a manner commensurate with the risks they pose (Australian Government Department of Health, Office of the Gene Technology Regulator, 2016). Four options are identified in this Australian review: (1) no amendment to the current regulations; (2) regulate certain technologies (including all site-directed nuclease techniques); (3) regulate some new technologies on the basis of the process used (excluding site-directed nuclease technologies that do not involve application of a DNA template); and (4) exclude certain new technologies from regulation on the basis of the outcomes they produce: that is, exclude if the genetic changes produced are similar to or indistinguishable from the product of conventional breeding (chemical and radiation mutagenesis and natural mutations). This last option, focusing on product rather than process, would again be similar to the recommendations of EASAC for the EU (Box 2): it is important to achieve international coherence in regulation.

2.2 Animal breeding in agriculture

Genome editing objectives in livestock breeding include improving animal health and improving agricultural traits. Recent examples of research to improve animal health include the following:

(1) To protect from porcine reproductive and respiratory syndrome, economically the most important disease of pigs in Europe, North America and Asia (Whitworth *et al*., 2016);

(2) To edit pig immune-system genes involved in the reaction to the haemorrhagic virus that causes African swine fever (ZFN-mediated in embryo editing of domestic pigs with the warthog RELA orthologue associated with resilience to African swine fever (Lillico *et al*., 2016)), a disease that has been hard to eradicate in sub-Saharan Africa and Eastern Europe (Ainsworth 2015, commenting on work in the UK Roslin Institute).

Other researchers have shown that the prion gene responsible for bovine spongiform encephalopathy (BSE) can be effectively modified by genome editing (Bevacqua *et al*., 2016). There is also significant interest in generating cattle resistant to trypanosome parasites[15], which are responsible for sleeping sickness, a serious problem for farmers in Africa.

Other proposed applications of genome editing of farm animals, addressing goals both to improve animal health and welfare and to improve agricultural traits, include genetic de-horning of dairy cattle for improved husbandry (Carlsson *et al*., 2016). Another opportunity is represented by the Belgian Blue, a natural breed of cattle selected for increased muscle, reduced fat and more tender meat, but where significant inbreeding has led to animal welfare problems. The desired trait arises from a mutation in the myostatin gene, which can be replicated by genome editing, demonstrated for cattle, goats, sheep and pigs (Charo, 2015; Crispo *et al*., 2015; Cyranoski, 2015; Wang *et al.* 2015). Thus, there is potential to avoid the negative effects of inbreeding and, if done in the right breed or in a controlled manner, to avoid problems during labour, which are also typical for the Belgian Blue. Thus, genome editing may enable a much more precise, faster approach to obtain the desired phenotype without other undesired traits co-segregating during natural selection. The genome of most livestock species has been sequenced and the costs of sequencing are becoming more affordable. The genome of a founder animal can, therefore, be fully sequenced to exclude the presence of off-target events as far as possible before release or marketing.

Other research ideas (Reardon, 2016) include the following:

- Generating chicken eggs without allergen, helping children who receive vaccines produced in chicken eggs.

[13] https://www.federalregister.gov/documents/2017/01/19/2017-00840/guidance-genome-editing-in-new-plants.
[14] http://blogs.fda.gov/fdavoice/index.php/2017/01/fdas-science-based-approach-to-genome-edited-products.
[15] https://clippings.ilri.org/2013/10/20/disease-resistant-cattle-for-Africa.

- Editing chickens to make them resistant to infectious diseases (such as avian influenza) and to produce only female offspring. This avoids the culling of male chicks, which are not required for egg production.

- Inactivation of genes for reproductive hormones in farmed fish, rendering them infertile, as a safety measure in case commercially approved, GM salmon or other farmed salmon[16] escape.

- Bees, one of the most important organisms for crop production, can be edited to add hygiene-associated genes so that colonies are less susceptible to mites, fungi or other pathogens.

A broad discussion of methodologies for animal breeding, including TALEN and CRISPR–Cas9, in the European context was published in 2014[17]. This assessment cross-references the Eurobarometer survey of public perceptions of GM animals, and notes societal issues: '*GM animals are perceived as far more problematic than GM crops*' in terms of potential risks, naturalness, usefulness and moral considerations. These problems may not be easily resolved by using newer approaches: '*Genome editing seems easier and quicker than transgenic modification. That does, however, not necessarily mean that genome editing is ethically neutral or will be easily accepted by consumers*'.

When considering the issues for animal welfare and for research objectives, it is important to appreciate that animal research using genome editing is already covered by the strict EU and Member State controls on animal research more generally and it is subject to the widely agreed principles of the '3 Rs' (replacement, reduction, refinement), in particular relating to 'refinement'. The scientific community needs to do more to engage with the public in discussing the issues. It would seem reasonable to conclude that there is a case for considering genome editing in livestock breeding as part of the toolbox for improving agricultural productivity and animal health if concerns about animal welfare or other ethics issues are tackled satisfactorily. The wider range of scientific and societal issues relating to farming animals is being discussed in the current EASAC project on 'Food and Nutrition Security and Agriculture'.

The EU regulation of genome editing in animals will be subject to the forthcoming decisions of Directorate-General for Health and Food Safety (DG Sante) on what is a GMO (see previous section). The advice of EASAC on plant breeding – to regulate the resulting trait rather than technology and to be transparent about what is being done – is also applicable to animal breeding. This view from EASAC is consistent with other recent conclusions (appertaining to genome editing in cattle), '*The products of editing should be subject to the same oversight as other food products, based on the results rather than the process that yields the results*' (Carroll *et al*., 2016). However, in the USA the FDA also recently published a draft revision to its previous guidance relating specifically to the regulation of intentionally altered genomic DNA in animals. In this draft guidance, the FDA proposes pre-market evaluation of genome-edited animals, effectively treating them the same as transgenic animals[18]. This regulation would not apply to non-food species that are raised in contained conditions, such as laboratory animals in research. The FDA proposal is open for public comments until April 2017 and is controversial because of the level of regulation proposed (Maxmen, 2017).

2.3 Other animal work

Other conceivable applications of genome editing in animal breeding (Reardon, 2016), such as to support the re-introduction of extinct species (woolly mammoth, passenger pigeon), or to generate more desirable pets (micro-pigs, koi carp with preferred colours and patterns, dogs with preferred behavioural traits), are beyond the scope of the present report.

2.3.1 Laboratory models

There are also considerable opportunities for using genome editing in developing cellular and animal models of human disease in laboratory research (Hsu *et al*., 2014; Smalley, 2016), including larger animal models[19]. As noted in the Statement by the German Academies (Leopoldina *et al*., 2015), the now feasible concurrent introduction of several targeted mutations can reconstruct complex disease pathways in model organisms and help identify and characterise therapeutic targets. Depending on the genetic modifications required, mouse models that would previously have taken 1–2 years to develop can now be created in months[20]. Advances using genome editing bring potential new models of neurological disorders such as autism, Alzheimer disease and Parkinson's disease in non-human primates, although these opportunities also emphasise the ethical challenges associated with animal welfare (Willyard, 2016).

[16] A recent study (Karlsson *et al*., 2016) shows that wild populations of salmon in areas in Norway with many salmon farms contained higher levels of farmed salmon DNA than those regions with less farming.
[17] Swedish University of Agricultural Sciences, http://www.slu.se/mistrabiotech/GManimalSymposium.
[18] http://www.fda.gov/downloads/Animal/veterinary/GuidanceComplianceEnforcement/GuidanceforIndustry.
[19] For example, the EU-COST action SALAM (Sharing Advances on Large Animal Models), International Society for Transgenic Technologies, http://transtechsociety.org/blog?p=1457. See also Nuffield Council on Bioethics (2016) and Barrangou and Doudna (2016) for discussion.
[20] Burton H, 3 February 2016 www.phgfoundation.org/blog/17136.

The US National Academies of Sciences, Engineering and Medicine of Science organised a workshop on gene editing under their initiative on Science and Welfare in Laboratory Animal Use (Institute for Laboratory Animal Research, ILAR). This wide-ranging workshop covered species-specific use of genome editing technologies in laboratory animals, regulatory issues, ethical issues and various stakeholder perspectives[21].

2.3.2 Xenotransplantation

Another application of genome editing in livestock is in xenotransplantation, the transfer of tissues and organs from animals to treat loss or dysfunction in humans. Research and societal interest in xenotransplantation has quite a long history and the fundamental issues were covered comprehensively in the Nuffield Council on Bioethics report of 1996. A project funded by Framework Programme 6, 'Xenome'[22], included a survey of public perceptions of xenotransplantation in several European countries.

There is clinical need for xenotransplants for patients with end-stage organ failure (heart, kidney, liver), but also for a variety of cell types, some of which are already being investigated as possible xenotransplants, such as liver cells (Nagata *et al.*, 2007), neurons (Leveque *et al.*, 2011), cornea (Hara and Cooper, 2011) and pancreatic islets (Elliott *et al.*, 2011).

A recent comprehensive review (Perota *et al*., 2016) discusses the immunological barriers to xenotransplantation[23], which especially apply to whole-organ transplantation. By elimination of a sugar epitope that is not present in humans (Gal-epitope) (Phelps *et al.*, 2003; Kang *et al*., 2016), the initial obstacle of hyperacute rejection (occurring within minutes) could be surmounted. It was the major factor behind recent successes with xenografted hearts (which survived more than 2 years) and kidneys (which survived up to 136 days) in non-human primates (Iwase *et al.*, 2015; Murthy *et al.*, 2016). Protection against delayed rejection (occurring within weeks), however, requires further modifications of the source animals, including expression of xeno-relevant transgenes and removal of xenoreactive non-Gal epitopes. The latter can be realised through genome editing (Li *et al.*, 2015), which also offers new opportunities to reduce the load of porcine endogenous retroviruses (Yang *et al.*, 2015). Further research is required to assess the long-term efficacy and safety of whole-organ xenotransplants, but tissue transplants such as porcine islets, which can be encapsulated, could soon enter the clinic. The first clinical trials using encapsulated neonatal porcine islets to treat type 1 diabetic patients have already been performed (Elliott *et al.*, 2011).

Regarding relevant legislation and regulations, clinical trials conducted within the EU using xenogeneic medicinal products are regulated by the European Medicines Agency (EMA). EMA guidelines on xenogeneic cell-based medicinal products (EMEA/CHMP/CPWP/83508/2009) came into effect in 2010. Detailed requirements for islet transplantation have recently been published (Cozzi *et al.*, 2016). The World Health Organization (WHO) had its first consultation on regulatory requirements for clinical xenotransplantation trials in Changsha, China, in 2008 and a second consultation in 2011 in Geneva, Switzerland, where it was concluded that principles and guidance contained in the Changsha Communiqué[24] remain valid and fully actionable. Further general EU expertise that may be relevant to assessing the products of genome editing in xenotransplantation is accruing from the Framework Programme 7 projects Translink (assessing risk factors associated with animal-derived bioprosthetic heart valve; www.translinkproject.com) and Xenoislet (developing transgenic pigs to treat type 1 diabetes; http://xenoislet.eu).

Recently it has been proposed that human organs destined for transplantation could be grown within pigs. Here too, genome editing is an important tool (Reardon 2015b; Perkel 2016) in possibly realising this objective. If a gene essential for the development of an organ, such as pancreas or heart, were inactivated by genome editing in the early embryo, the developing foetus would lack the organ. But if (induced) pluripotent stem cells were introduced into the embryo, then these could participate in foetal development, compensate for the defect in the host embryo and produce the organ. This type of complementation has been achieved with embryos and stem cells of the same species (pig; Matsunari *et al.*, 2013) and between closely related species (mice and rats; Kobayashi *et al.*, 2010). The resulting animal is a chimaera consisting of cells from the embryo and the injected stem cells. It remains to be seen whether such a scheme would work with more distantly related species such as humans and pigs. Preliminary experiments to investigate this are currently underway in various laboratories around the world[25]. Because of the ethical issues, a vital part of this work is devising the means to restrict the developmental potential of the injected human induced pluripotent stem cells to avoid any contribution to the chimaera beyond the organ to be transplanted. This restriction potentially can be achieved by inactivation of specific developmental genes through genome editing.

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[21] December 2015 ILAR Roundtable http://nas-sites.org/ilar-roundtable/roundtable-activities-gene-editing-to-modify-animal-genomes-for-research/webcast.

[22] *Xenotransplantation between medicine and society*, http://www.observa.it/gli-xenotrapianti-tra-medicina-e-societa/?lang=en.

[23] These include hyperacute rejection, acute humoral xenograft rejection, immune cell-mediated rejection and instant blood-mediated inflammatory rejection.

[24] The Changsha Communique 2008 on http://www.who.int/transplantation/xeno/ChangshaCommunique.pdf.

[25] Curie J. *US lab attempting to grow pig embryos with human pancreases*, Bionews 13 June 2016; http://www.bionews.org.uk/page_658075.asp.

3 Gene drive in modification of populations in the wild

3.1 Use of gene-drive-based technologies

Gene drive is a process of biased inheritance that allows a gene to be transmitted from parent to offspring at an increased rate. As a result, the gene can increase in frequency in a population over multiple generations. Gene drive systems are hence 'self-sustaining': this is the key differentiating characteristic from other forms of genetic modifications, which are applied either only to one generation or are eventually selected out, if disadvantageous, over a few generations.

Currently gene drive studies are focused on the genetic modification of wild populations of some particularly harmful species, such as disease vectors. Gene drive has been proposed as an efficacious tool to address several major public health challenges, including the transmission of malaria, Zika and dengue fever by mosquitoes (Gantz *et al*., 2015; Alphey, 2016; Hammond *et al*., 2016). Other potential applications for gene drive (Reardon, 2016) include editing ticks so that they are unable to transmit bacteria that cause Lyme disease, and editing aquatic snails to prevent them from transmitting the parasitic disease schistosomiasis.

There is considerable interest in the potential benefits of gene drive systems. A recent UK House of Lords Science and Technology Committee report on GM insects (2015) highlights the possible value of gene drive systems to eradicate disease-carrying vectors that affect crops and people. Potential applications (in addition to malaria, Zika and dengue) are suggested to include containment of chikungunya, West Nile fever and Chagas disease, together with various applications for sustaining agriculture (e.g. tackling bluetongue disease, equine infectious anaemia, infectious salmon anaemia, Mediterranean fruit fly). The UK is a leader in research and innovation on GM insects, including gene drives (with growing competition by the USA and China making considerable recent investment), but public awareness of the scope and potential of these technologies is yet to be mapped. This parliamentary report calls for increased public investment in GM insect field trials to test the science, promote public engagement and lead international developments.

While the potential and promise of gene drive technology is significant, the research is still at a relatively early stage. Some groups have expressed concerns about the potential risks of using gene-drive-based technology[26]. However, as noted by the recent report by the US National Academies of Sciences, Engineering and Medicine (National Academies, 2016b) in their review of gene drive opportunities and challenges, it is essential to continue research to establish the efficacy and safety of gene drives before it can be decided whether they are suitable for use. The report concluded that the significant potential of this application justifies proceeding with phased research and testing so that benefits and risks can be properly assessed. The US National Academies recommendations are summarised in Box 3.

3.2 Challenges and limitations to use of gene-drive-based technologies

There are some specific issues that could hinder the efficacy of a gene drive system in some populations. For example, efficacy would be compromised if genetic diversity in natural populations provides sources of natural resistance to the gene drive (Deredec *et al*., 2008; Unckless *et al*., 2015). Researchers will also need to examine the possible risk of resistance stemming from the genetic modification as a possible limit on long-term

Box 3 Summary of US National Academies recommendations on gene drive

1. Funders of gene drive research should coordinate to reduce gaps in knowledge about the molecular biology of gene drives and other critical research areas including population genetics, evolutionary biology, ecosystem modelling, ecological risk assessment and public engagement.
2. Funders of gene drive research should establish open access repositories of data and standard operating procedures for gene drive research: to share knowledge, and guide both risk assessment frameworks and research design and monitoring standards.
3. Key characteristics of gene drives – including their intentional spread and potential irreversibility of environmental effects – should be used to frame societal appraisal of the technology.
4. Robust ecological risk assessment must be part both of field trials and environmental release of gene drive-modified organisms.
5. Conducting risk assessment and making policy decisions must involve public engagement.[27]
6. Selecting sites for field testing and environmental releases should be guided by scientific judgement, feasibility of risk assessment and opportunity for community engagement. Preference should be accorded to locations in countries with existing scientific capacity and governance frameworks to conduct and oversee safe investigation of gene drives.

Source: adapted from National Academies (2016b).

[26] For example, the International Union of Conservation of Nature (IUCN) has recently called for a moratorium on gene drive research until further assessment of the impact on conservation can be made: http://portals.iucn.org/congress/motion/095. In other developments, a recent meeting of the United Nations Convention on Biological Diversity rejected calls for a global moratorium on gene drives but instead encouraged caution in field testing the products of synthetic biology, including gene drives, with better risk assessment of potential effects (Callaway, 2016c).

[27] See, for example, Anon. (2015) and Reardon (2016).

efficacy of specific applications of gene drive approaches. More research is also needed to assess genetic stability in the wild: that is, the impact of alternative DNA repair pathways (Alphey, 2016), and there are efforts to engineer practical gene drive systems designed to select against the emergence of drive-resistant alleles (Noble *et al*., 2016).

In addition to efficacy questions, the recent increased interest in gene drive has led to questions about the potential safety of such a technology. Concerns have been raised that the spread of gene drive constructs may be difficult to control and might have ecological consequences attributable to reduction in the population of the target species (which is a question relevant to all vector control interventions) or spread of genes to other species beyond those intended. These questions will need to be addressed through safety studies and a risk assessment for each application of gene drive. Prior modelling of the manipulation of natural populations is likely to be an essential part of research studies, and there will need to be extensive risk assessment to consider the possible consequences for ecosystems and to substantiate use of remediation measures. Given the variety of ways gene drive could be applied, safety concerns need to be related to a specific product and cannot be realistically assessed on general terms. Ultimately all products should be subject to a thorough risk assessment that will take into account the characteristics of the product developed, its intended use and the conditions of use.

The second concern often expressed is about the risks linked to an accidental escape of a gene drive organism. This concern is not unique to gene drive research but the self-sustaining nature of the technology makes it an important consideration. Several control and containment measures have been suggested to curtail the accidental spread of a modified organism if escaped from laboratory research containment (Akbari *et al*., 2015). In addition, ecological containment – whereby laboratory research is performed where there is no natural population of the same insect in the region, so that interbreeding is not possible if the modified insect escapes from the research facility – offers additional safeguards. Some have suggested the possibility of using molecular confinement methods (DiCarlo *et al*., 2015). It has been suggested that it could be possible to develop a drive system to overwrite a previous one, which would act as a safeguard mechanism (Wu *et al*., 2016), but this has not yet been fully explored.

3.3 Regulation of gene-drive-based technologies

One of the main challenges to the development of gene-drive-based products is regulatory. Some of the novel aspects of the technology may require clarifications and adjustments in current regulatory frameworks. Several reports, including those of the US National Academies of Sciences, Engineering and Medicine and the UK House of Lords, have mentioned this topic. Options for legal regulation of gene drives are also discussed in detail in several publications (for example, Oye *et al*., 2015; Champer *et al*., 2016)[28].

The report from the UK House of Lords noted that the existing regulatory regime for GMOs could be a basis for regulating GM insects, with ongoing monitoring of advances in research needed to ensure the framework remains fit for purpose. The House of Lords report noted two challenges: the importance of integrating the consideration of benefits into risk assessments; and the new question of persistence posed by the application of gene drive technology, which would require specific consideration and the stipulation of monitoring requirements. Outside the UK and USA, other countries have begun to review their regulatory frameworks to ensure they are fit for purpose. For example, Australia began a review process in December 2016.

The EASAC Working Group observed that, because gene drive is further into the future than some of the other fields of application of genome editing, there is time to consider the issues while R&D continues under frameworks that consider the potential risks in a stepwise fashion and are built on extensive stakeholder engagement. Research groups such as Target Malaria are already following these recommendations and are reaching out to stakeholders as a core pillar of their activities[29].

There are many possible applications of gene drive technology and it will be important to consider for each the cost/benefit of the proposed application and to compare it with other methods aimed at controlling the targeted species. At the present time, the research is largely focused on addressing key public health issues such as malaria, where the current harm inflicted by the target species would be an important consideration in assessing the use of a gene-drive-based technology. It is also important to note that efforts to construct adaptable governance policies can draw on existing guidelines, particularly the WHO Guidance Framework for Testing of GM Mosquitoes, to facilitate the necessary international coordination and collaboration. Gene drive should be regarded as complementary to other approaches to controlling infectious diseases and invasive pests, helping to provide an additional tool for improving public health and conservation.

[28] In January 2017 the US FDA also provided draft guidance for industry on mosquito-related products, seeking to clarify whether such products should be regulated as 'new animal drugs', while also emphasising the FDA principle to maintain product-specific, risk-based regulation (see footnote 14).

[29] Target Malaria (http://targetmalaria.org) and the discussion of gene drive approaches for controlling malaria vectors in Africa (http://aasciences.ac.ke/updates/events/using-gene-drive-approaches).

4 Micro-organisms

Genome editing augments, and might simplify, the existing and extensive technology already available for the genetic alteration of micro-organisms. However, it offers genetic access to prokaryotic species and some parasites and fungi that have been more refractory in this respect. Homologous recombination has led to extensive natural and laboratory-generated gene exchange between micro-organisms (involving transformation of DNA, by transduction or conjugation). In the view of the EASAC Working Group, therefore, genome editing in microbes raises no new ethical issues or issues for regulatory frameworks. Generally, the EU regulation of genome-edited microbes will be subject to the established rules for contained use and deliberate release of GMOs, and dependent on the ongoing legal analysis by DG Sante of what is a GMO.

4.1 The bioeconomy

There are various applications of genome editing in microbes already underway or envisaged as a basis for programmable and high-throughput functional genomics (Selle and Barrangou, 2015). The following are some examples:

- Applications in producing third-generation biofuels in bacteria, fungi and microalgae (Liao *et al*., 2016), exemplified by modified yeast degradation of wood xylose for biofuel as discussed in the German Academies statement (Leopoldina *et al*., 2015).

- Modified yeasts may also be employed in food production, for example to enhance flavour in beer, but again there are implications for doing this according to whether the edited-yeast beer would be counted as a GM food (Callaway, 2016b).

- Potential opportunities for microbial modification in bioremediation, although uses of modified microbes outside contained facilities may raise environmental concerns.

- Genome editing of microbes in contained use to underpin novel approaches to generating pharmaceuticals or other high-value chemicals (Smanski *et al*., 2016), potentially reinvigorating drug discovery pipelines and establishing new routes for synthesising complex chemicals. For example, editing to increase mevalonate production in yeast facilitates a key step in synthesising anticancer drugs (Jakociunes *et al*., 2015).

- Application of CRISPR–Cas may also be valuable in generating novel antimicrobial agents, conferring abilities to avoid drug resistance and the indiscriminate killing of harmless, or even beneficial, bacteria (Citorik *et al*., 2014; Barrangou and Doudna, 2016). As well as novel antivirals and antibacterials, there are opportunities for vaccines and drug discovery to tackle intracellular parasites such as *Plasmodium* and *Toxoplasma* species (Carrasquilla and Owusu, 2016).

- Potential applications of edited microbes as sensors of human disease signals such as inflammation (Tauxe, 2015).

- Enabling the recording of defined biological events into stable genetic memory, with proof of principle demonstrated for CRISPR–Cas-edited *Escherichia coli* (Shipman *et al*., 2016). Expanding DNA data storage capacity provides a strategy to generate intrinsic devices within various cells that autonomously record the timing of complex and inaccessible processes such as gene dysregulation in cancer. Linking DNA memories with the power of cells to sense and act on their environment could lead to considerable advances in synthetic biology (Borkowski *et al*., 2016).

4.1.1 Synthetic biology

Many of the regulatory issues for microbial genome editing research and innovation fall within the scope of what is regarded as synthetic biology. A previous EASAC report on synthetic biology (2010) covers some relevant general points for regulation, codes of conduct, models of open science and benefit-sharing, skills development and the EU bioeconomy, although it predates the newest phase of genome editing. In the Working Group's opinion, the advance of genome editing does not alter the conclusions reached in that earlier report. The European Commission's scientific committees recently completed their advice on synthetic biology following extensive public consultations (SCENIHR, SCHER and SCCS 2016). This advice covers microbial genome editing, concluding, with respect to environmental risks, that the increasing speed of modification of micro-organisms by genome editing might pose challenges to risk assessment capacity while not in itself creating new risks. The recent discussions in the Convention on Biological Diversity (CBD) about synthetic biology have also encompassed genome editing, including gene drive (UNEP, 2015),

within the terms of the operational definition[30]. These ongoing CBD discussions are highly relevant to global governance of the environmental aspects of genome editing.

4.2 Biosafety

Concerns have been raised about the possibility that genome editing research could be conducted outside regulated laboratory settings, for example by 'biohackers' in the DIY biology community (Ledford, 2015a). The equipment and reagents are readily available but there is no evidence that genome editing is much used yet by DIY biologists (Kuiken, 2016). Moreover, it has been said that there is no *a priori* reason to expect the DIY community to cause more harm when using genome editing than anyone else, and DIY biologists must similarly conform to established biosafety legislation. The DIY community has been active in developing norms and a code of conduct[31] to support a proactive culture of personal responsibility (Kuiken, 2016). EASAC supports a proposal made in previous IAP discussion that the Global Young Academy (https://globalyoungacademy.net) should assess the issues for DIY research that is being conducted outside conventional laboratory settings.

4.3 Biosecurity

In the recent report by the Nuffield Council on Bioethics (2016), the technology of genome editing was described as transformative. While it can be argued that this might be the case for the modification of eukaryotic organisms, in the view of the Working Group genome editing merely augments and simplifies technology already available for the modification of microbes. Therefore, it is questionable to what extent it leads to new concerns about deliberate misuse of genome editing in state-sponsored research or for terrorism. For example, the recent annual threat assessment of the US intelligence community[32] includes genome editing in a discussion of weapons of mass destruction and proliferation, observing, '*Given the broad distribution, low cost, and accelerated pace of development of this dual-use technology, its deliberate or unintentional misuse might lead to far-reaching economic and national security implications*'. PCAST, the group of science and technology advisers to the US President, recently recommended developing a new biodefense strategy, in part because of perceived dangers posed by new technologies such as CRISPR[33].

It remains to be ascertained whether microbial genome editing raises significant new issues for harm to human, animal or plant health relevant to the Biological and Toxin Weapons Convention (BWC)[34]. The accuracy of genome editing may accentuate some current issues for the scientific underpinning of the BWC. For example, article VII of the BWC stipulates that mutual aid should be given in cases of suspected attacks with modified organisms. Genome editing might, therefore, have implications for developing adequate microbial forensics to detect, characterise and track infectious disease outbreaks to distinguish between deliberately induced and natural epidemics. Examples of genome editing have been reviewed by the IAP Biosecurity Working Group[35] in their discussions of science and technology developments relevant to the BWC, and it is important that the scientific community continues to advise policy-makers during the current process of review of the BWC: EASAC aims to continue supporting discussion of biosecurity and other aspects of genome editing.

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[30] Definition recommended by CBD Subsidiary Body on Scientific, Technical and Technological Advice (https://www.cbd.int/doc/recommendations/sbstta-20/sbstta-20-rec-08-en.doc); '*Synthetic biology is a further development of modern biotechnology that combines science, technology and engineering to facilitate and accelerate the understanding, design, redesign, manufacture and/or modification of genetic materials, living organisms and biological systems*'.

[31] https://diybio.org/codes.

[32] Clapper JR, 9 February 2016, on http://www.dni.gov/files/documents/SASC_Unclassified_2016_ATA_SFR_Final.pdf.

[33] https://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/pcast_biodefense_letter_report_final.pdf.

[34] There might also be biosecurity concerns arising from intended misuse of gene drive systems (Oye *et al*., 2015; Champer *et al*., 2016), deliberately spreading human, animal or plant diseases. There have been calls for a restriction on access to information on gene drives to prevent misuse for malicious purposes (Gurwitz, 2014), but this would probably be both ineffective and counter-productive in hampering attempts to enhance biosecurity (Oye and Esvelt, 2014).

[35] See www.iapbwg.pan.pl/index.php and https://royalsociety.org/topics-policy/projects/biological-toxin-weapons-convention ('The Biological and Toxin Weapons Convention. Implications of advances in science and technology') for discussion of the issues at the Warsaw 2015 meeting.

5 Human health: somatic and germline cell applications

Applications of genome editing described in the previous chapters are all potentially relevant to human health objectives. However, much of the debate elsewhere on genome editing with regard to human health has focused on gene editing in human cells, which will be the focus of the present chapter. Considerable progress is being made in basic research in taking a genome-wide and cell-systems approach in the use of genome editing to elucidate causal linkages between genetic variation and biological function and to perform functional genomic screens (Hsu *et al*., 2014). It is not possible in our report to review all such research advances, but their breadth is illustrated in research using the CRISPR–Cas system that includes the following:

- Identification of essential genes in human cells (and tumour-specific vulnerabilities) (see, for example, Hart *et al*., 2015; Osario *et al.* 2015).
- Reprogramming of adult cells into stem cells (Howden *et al*., 2015).
- Prevention of flavivirus reproduction without disrupting the host (Zhang *et al*., 2016).
- Studying the influence of epigenetics on regulatory functions and cellular reprogramming (Ledford, 2015b; Kungulovski and Jettsch, 2016) including in the brain (Bailus *et al*., 2016).

When considering these opportunities and the requisite regulatory framework, there is critical need to distinguish between the use of genome editing in the basic research context and in the clinical application, and between its use in somatic cells and in germline cells. However, one general problem perceived when reviewing country policies towards genome-related technologies (Isasi *et al*., 2016) is the vagueness encountered in basic definitions and in distinguishing between clinical and research applications. For example, in some countries there is considerable uncertainty about whether existing bans on genetic engineering in embryos and other germline cells for clinical purposes also encompass prohibition to conduct basic research (Isasi *et al*., 2016). The conclusions from the FEAM workshop (Academy of Medical Sciences, 2016; FEAM, 2017) also emphasised the need to develop and share common definitions: for example, the definition of 'embryo' varies across Europe, which may relate to varying value assumptions.

As emphasised in the Statement by the German Academies (Leopoldina *et al*., 2015), support for putative applications in human germline interventions that have an impact on the genome of offspring requires more research both to understand complex interactions between genes and to understand the molecular mechanisms involved in editing, in order to increase efficiency, selectivity and safety. As discussed in the Statement of the Hinxton Group (2015; an international, interdisciplinary consortium on stem cells, ethics and law), safety research is important to clarify both the extent and impact of off-target events (unintended genetic alterations)[36], interaction between individual gene functions, and mosaicism (genetic variation across cells). This knowledge is required to improve even further the fidelity of genome editing. Such research also requires improving *in silico* tools to predict off-target effects and whether they are likely to be deleterious, and to guide design in genome editing.

Recent findings in the USA from a Pew Research survey (Funk *et al*., 2016) epitomise the current mix of excitement and concern in the general public. Almost 70% of respondents to the survey said that they were 'very' or 'somewhat' worried about use of genome editing technologies *in utero* to reduce a child's risk of serious disease, with about 50% indicating they were enthusiastic about such a use: three in ten respondents were both enthusiastic and worried. Patient-group representatives in Europe are eager to see genome editing progress (FEAM, 2017). For example, in a survey by Genetic Alliance UK, more than 75% of respondents, those with a genetic condition or family members, supported the use of genome editing technology but made a clear distinction between tackling medical conditions (where it was supported) and the enhancement of physical or cognitive attributes in healthy people (where it was not supported)[37].

5.1 Slippery slope, risk and proportionality

Does genome editing represent a 'slippery slope'? In general terms, the slippery slope describes how a technology may be introduced that seems morally acceptable or even laudatory in dealing with a problem but the technique is then extended to further areas or problems, ending up by application in a way that is

[36] Recent research (see Box 1 and Kleinstiver *et al*., 2016; Slaymaker *et al*., 2016) suggests that engineered Cas9 nucleases as alternatives to CRISPR–Cas9, for example eSpCas9, SpCas9–HF1, may significantly reduce 'off-target' editing. Furthermore, recent research has crafted a genome editing 'toolbox' capable of targeting multiple genes while limiting unintended effects, by turning the Cas9 system off once it has accomplished its intended task and before editing off-target sites (Cao *et al*., 2016)

[37] 'Genome editing technologies: the patient perspective', 23 November 2016; on https://www.geneticalliance.org.uk/media/2623/nerri_finalreport15112016.pdf.

morally objectionable. To prevent this, some contend that the technique should not be applied in the first instance. However, this argument is based on two assumptions: (1) that the slope is slippery such that extension of the technique cannot be prevented; and (2) that the end of the slope is ethically objectionable. Therefore, it is vital to ensure that ethical evaluation of the final state is robust and it is also essential to consider whether the slope can be made less slippery. In the case of genome editing, the nature of the slippery slope may encompass the difficulty in defining multiple boundaries, between basic, translational and clinical research as well as boundaries between tackling severe or other diseases, non-therapeutic purposes (biological enhancement) and eugenics.

Assessment of risk–benefit may be an important factor in deciding whether to embark on what may be perceived as a slippery slope, and in knowing when to stop. However, there are again difficulties in terminology in assessing risk and benefit, as discussed in other contexts in previous EASAC work (EASAC, 2015b). 'Risk' is sometimes used synonymously with 'negative outcome', sometimes with 'the likelihood of a negative outcome'. Furthermore, because of gaps and uncertainties in our knowledge, the comparison of risk and benefit may involve incommensurate elements. Multi-stakeholder dialogue is one way of assessing the risks and benefits while taking account of differing perspectives in valuing risk and benefit, but such assessment should not be made 'once and for all'—we must be prepared to revise assessments if the evidence or values change.

The need to apply the principle of proportionality when considering risks of emerging technologies, and the relationship between the proportionality and precautionary principles, is discussed in detail by Hermeren (2012). As noted by EASAC work in other contexts (EASAC, 2015b), if considering applying the precautionary principle, it is equally necessary to understand the risks of not embarking on new work, namely the benefits that may be lost to society by deterring research and innovation. When assessing the proportionality of an approach, three questions should be asked (Hermeren, 2012):

1. Is the approach relevant to bring about or help achieve the goal?

2. Is it the most favourable option; that is, could there be a less controversial or risky means to attain the goal?

3. Are the means excessive in relation to the intended goal?

Although these considerations may be relevant to all applications of genome editing, when interpreted in terms of human health outcomes they may be regarded as most tangible for human-cell editing. Thus, the issues are raised here as the prelude to discussion of human-cell modification.

5.2 Biomedicine/somatic changes

Potential somatic cell applications include gene- and cell-based therapies. The new approach to gene therapy has expected advantages over previous, vector-mediated, gene delivery, for example by circumventing concerns about the safety of the viral vector. Further detail on the range of clinical research in somatic cells (and in autologous induced pluripotent cells) is provided in the FEAM review of the current landscape (Academy of Medical Sciences, 2016) and the outputs from the International Summit on Human Gene Editing (National Academies, 2016a) and the FEAM workshop (FEAM, 2017).

One of the first clinical examples of genome editing (using the ZFN technique) was modification of the *CCR5* gene in T cells to treat patients with HIV. A subsequent example, the treatment of a child with acute lymphoblastic leukaemia using TALEN-modified donor immune cells, has aroused significant public interest. Research is now moving from the study of individual responses to controlled clinical trials.

Although *in vivo* human genome editing trials started in 2016, for example on factor IX therapy of haemophilia B (Reardon, 2015a; and see Academy of Medical Sciences, 2016), it is currently easier to envisage *ex vivo* treatment (modification of the patient's cells in the laboratory and returning them after propagation to the patient) because direct delivery of genome editing tools to tissue within the body presents challenges for specific and efficient targeting (Caroll and Charo, 2015). The first phase I CRISPR–Cas9 trial has started in China, enrolling patients with metastatic non-small-cell lung cancer (where chemotherapy, radiation therapy and other treatments have failed) (Cyranoski, 2016). T cells are extracted from the blood of enrolled patients and CRISPR–Cas9 is used to knock out the gene that encodes PD-1 protein (normally acting as a constraint on the cell's capacity to launch an immune response) before returning the T cells to the patient. A related study proposal (to treat myeloma, melanoma and sarcoma, but with other edited modifications in addition to PD-1 knockout) has been approved in the USA by the National Institutes of Health (NIH) Recombinant DNA Research Advisory Committee.

In the EU, the general regulatory procedures for such clinical research are clear. The European Commission Regulation (EC) 1304/2007 on advanced therapy medicinal products (gene, cellular and tissue based) sets out EU requirements for therapies and standards for

clinical trials. A single centralised assessment procedure run by the EMA covers safety, efficacy and quality of products developed: further detail of the regulatory frameworks is provided in the FEAM review (Academy of Medical Sciences, 2016). However, the output from the FEAM workshop (FEAM, 2017) noted that preparation of specific regulatory guidance would require ongoing dialogue between regulators and researchers from both the academic and commercial sectors.

As with other innovation in healthcare, these advances raise questions as to whether benefits will be distributed equitably (or differently from existing treatments) and in what ways the interests of people in vulnerable groups may be affected.

5.3 Reproduction/germline changes

Genome editing of the germline (this includes germ cells and early embryos) has potential applicability to avoid inherited genetic disease. Although there are already some other options for preventing familial disease – in particular pre-implantation genetic diagnosis – there are circumstances in which these other, established, methods would not be effective (Nuffield Council on Bioethics, 2016). Monogenic diseases may individually be rare but in aggregate there are many thousands of rare diseases (www.omim.org) and the WHO estimates that the prevalence of all single-gene disorders at birth is approximately 1% worldwide[38].

Making human genetic changes heritable is not currently allowed by national legislation in any Member State[39], nor may it be financed by EU research. The European Commission should, nonetheless, take note of what is being discussed and proposed outside the EU.

Recent Chinese research on human embryos, including modification of the gene of beta-globin responsible for the blood disorder beta-thalassemia via the CRISPR–Cas 9 system (see Academy of Medical Sciences, 2016 for further detail), has stimulated extensive discussion on what research and applications should be allowed. There have been various proposals for a moratorium, for example, from the United Nations Educational Scientific and Cultural Organization (UNESCO) International Bioethics Committee[40], and the FEAM review (Academy of Medical Sciences, 2016) provides a comprehensive account of European and other international statements on human germline genome editing. The European Group on Ethics in Science and Technology (EGE, 2016) also concludes that there should be a moratorium on gene editing of human embryos or gametes that would result in the modification of the human genome. The EGE cautions on whether a clear distinction can be made between basic and translational research, and this difficulty in defining boundaries has implications for what research may be permitted or would fall within the scope of a moratorium.

The German Academies statement (Leopoldina *et al*., 2015) endorses suggestions for an international moratorium on all forms of human germline engineering that could have an impact on the genome of offspring. From these Academies' perspective, the moratorium would provide an opportunity to discuss unresolved questions and develop recommendations for regulation, but it should not constitute a general restriction on methodological developments and limit any promising new genome editing approaches. In some EU Member States, research can be conducted on germ cells and human embryos up to 14 days

Box 4 Some ethical considerations in human germline applications

1. Safety.
2. Dignity, with regard to the boundary between treatment and design. Although this distinction is not always clear cut, designing enhanced functions might be perceived to jeopardise the genetic integrity of all human beings, bring concerns for the welfare of the child, and may accentuate equity and proportionality concerns.
3. Justice, with regard to equity in the sharing of benefits.
4. Proportionality: see section 5.1.
5. Autonomy: the right of individuals to decide as long as nobody else is harmed.

Sources: UNESCO, Hinxton Group and European Group on Ethics in Science and Technology, Nuffield Council on Bioethics[41] and EASAC Working Group discussion.

[38] http://www.who.int/genomics/public/geneticdiseases/en/index2.html.

[39] UK regulations allowing mitochondrial replacement therapy, to correct faulty mitochondrial DNA, came into force in October 2015. However, in the passage of the enabling regulations, the government minister explicitly asserted that the UK Government did not regard the procedures as producing 'genetic modification' (Earl Howe, Hansard, HL Deb 5 February 2015; cited as footnote 181 in Nuffield Council on Bioethics, 2016).

[40] 'Updating its reflection on the human genome and human rights' calls for a moratorium on germline applications and hereditary modifications. In surveying the legislative position worldwide, 29 of 39 countries reviewed by UNESCO had a ban on editing the human germline. In 25 countries, the ban was legally binding, 4 had guidelines, not laws (China, Japan, Ireland, India) while rules in the remaining 10 countries were ambiguous.

[41] In their wide-ranging analysis, the Nuffield Council on Bioethics (2016) broadly identify additional key moral perspectives that inform attitudes to different potential applications of genome editing. These include the following: science as a moral enterprise, moral conservatism, and moral norms and human rights (see their report for further detail).

after fertilisation of the egg cells[42], when justified and supported by rigorous scientific and ethical review. After this period, embryos are discarded and there are no genetically engineered offspring. Genome editing research in human embryos is now approved in the UK (Academy of Medical Sciences, 2016) and Sweden (Callaway, 2016a). The recent success of research on culturing human embryos up to 13 days (Shahbazi *et al*., 2016) indicates the possibility of further research on human embryo development and may re-open the debate on whether legislation should be amended to allow embryo research *in vitro* to continue for longer than the current legal limit of 14 days.

Although ethical and legal aspects (see Box 4) are a national/local responsibility for EU Member States, the EU Clinical Trials Directive 2001/20/EC and Clinical Trials Regulation EU No. 536/2014 (effective after May 2016) include the provision '… *no gene therapy trials may be carried out which result in modifications to the subject's germ line genetic identity*'. The ethics committee of the French national biomedical research agency INSERM (Institut national de la santé et de la recherche médicale) recently called for a review of the ban on all genetic modifications to the human germline as part of a wider initiative that should also act to promote open debate on the societal aspects of genome editing technologies (Hirsch *et al*., 2017).

Although germline clinical applications are currently not allowed, further consideration of the issues for deciding future options has to take account of the wide spectrum of possible interventions: from avoidance of serious disease-causing mutations to biological enhancement. Where might the boundary be for any moral obligation to treat/avoid disease? It should also be noted (Mathews *et al*., 2015) that use of genome editing, if permitted in basic research on human sperm, eggs and embryos, could yield insight, for example, on how cell types are specified in the early human embryo, understanding biology and genetics of stem cell lines, and on the role of specific genes in the differentiation of sperm and eggs and the development of diseases.

Some germline modification objectives will be more controversial than others (even in a well-regulated context): technical and safety concerns may be resolved by scientific research, but moral considerations require ethics and other humanities research and public debate. It has been suggested (Mathews *et al*., 2015) that national academies are well placed to take the lead on efforts to ensure that debates on applications of genome editing are geographically and demographically inclusive and inform policy discussions.

Active discussion in this area raises some practical questions for the scientific and policy-making communities. It is of great importance that the issues identified in discussion on somatic and germline cell genome editing by the academy initiatives (International Summit on Gene Editing (National Academies, 2016a) and the FEAM review (Academy of Medical Sciences, 2016); FEAM, 2017; and the work by individual member academies of EASAC) should reach a wider audience. Although these academy-led activities are not yet complete, EASAC endorses the interim conclusions from the International Summit on Gene Editing (National Academies, 2016a)[43], which include the following:

- *Basic and preclinical research.* Intensive research is clearly needed and should proceed subject to appropriate legal and ethical rules and oversight. If, in the process of research, early human embryos or germline cells undergo genome editing, the modified cells should not be used to establish a pregnancy. In view of the divergent views at the national level across the EU on the acceptability of embryo research, it is acknowledged that the decision by the European Commission not to fund research on embryos will be unlikely to change at present (FEAM, 2017).

- *Clinical use: somatic gene editing.* There is need to understand the risks, such as inaccurate editing, and the potential benefits of each proposed genetic modification. These applications can and should be appropriately and rigorously evaluated within existing and evolving regulatory frameworks for gene therapy—in the EU by the EMA and national agencies.

- *Clinical use: germline interventions.* These applications pose many important issues,

[42] Making genetic changes in early embryos, for example to study disease processes or to improve outcomes of in vitro fertilisation depends on the law of the Member State. Where it is allowed, it is subject to rigorous scientific and ethical review. Research on surplus embryos is allowed (normally to a 14-day limit) in 16 Member States, forbidden in 4 and undefined in 8: answer given by Commissioner Moedas to question in the European Parliament, E-003329/2016; 28 June 2016; http://www.europarl.europa.eu/sides/getDoc.do?type=WQ&reference=E-2016-003329&language=EN. Where such research is permitted, the use of research material in humans even for treating patients is expressly prohibited. Most Member States have ratified the Oviedo Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine which, *inter alia*, prohibits intentional human germline modification and the creation of human embryos for research purposes. The FEAM review (Academy of Medical Sciences, 2016) provides a comprehensive account of the current situation in Member States with respect to national regulatory frameworks covering the use of embryos in genome and other research.

[43] After the first Summit in December 2015, the National Academies have organised further meetings (February–July 2016) to engage with stakeholder groups, discuss governance perspectives, the issues for race and genetics in US history and the intersection of moral views and public policy. Material from the presentations in these subsequent discussions is available on http://nationalacademies.org/gene-editing.

including the risks of inaccurate or incomplete editing, the difficulty of predicting harmful effects, the obligation to consider implications for both the individual and future generations who will carry the genetic alterations, and the possibility that 'enhancements' to subsets of the population could exacerbate social inequities or be used coercively. It would be irresponsible to proceed unless and until the relevant safety and efficacy issues have been resolved and there is broad societal consensus about the appropriateness of the proposed application.

- *Need for an ongoing forum.* The international community should strive to establish norms for acceptable uses of human germline editing and to harmonise regulation. EASAC welcomes the opportunity to help in taking the discussion forward and engaging with additional audiences.

6 Conclusions and recommendations

Genome editing, the deliberate alteration of a selected DNA sequence in a cell, is a very important toolset in fundamental research to understand biological processes and disease. Genome editing has been described by some (for example, the Nuffield Council on Bioethics, 2016) as a transformative technology and, certainly, in some areas of research and innovation, it is transforming expectations and ambitions. Genome editing has the potential to deliver precise nucleotide changes. Taken together with the growing ability to monitor and avoid off-target effects, it brings new opportunities within range. Because of its general applicability (in microbes, and plant, animal and human cells) it has a very wide range of potential uses to tackle societal objectives and to accelerate innovation in the bioeconomy. These potential applications include gene- and cell-based therapies to control diseases and in reproduction to avoid the inheritance of disease traits, the control of vector-borne diseases, improved crop and livestock breeding, including improved animal health and welfare, modifying animal donors for xenotransplantation, and industrial microbial biotechnology to generate biofuels, pharmaceuticals and other high-value chemicals, among other possibilities.

Present knowledge gaps and uncertainties emphasise the need for more basic research. We expect that research advances will fill many of the knowledge gaps referred to previously in our report and that progressive refinement of genome editing tools will further increase their efficiency and specificity, thereby reducing off-target effects. Given the increasingly widespread use of genome editing, the research community should consider how best to maintain an accessible database of modifications undertaken – although it would be a challenge to be comprehensive – and what the necessary quality control procedures are to inform future research. We anticipate that the fast pace of change in research and innovation will continue, and EASAC is willing to return to the subject of this report in due course to review our assessments.

EASAC concludes that policy considerations should focus on the applications in prospect rather than the genome editing procedure itself as an emerging technology. It is important to ensure that regulation of applications is evidence-based, proportionate and sufficiently flexible to cope with future advances in the science. In the following paragraphs we summarise our main sector-specific recommendations from the preceding chapters and add some general conclusions.

Plants

The increasing precision now possible in plant breeding represents a big improvement compared with conventional breeding approaches relying on random, uncontrolled chemical- or radiation-induced mutagenesis and on intra- or interspecific crossings with random distribution of genes or alleles. We reaffirm our recommendations from the previous EASAC work on new plant breeding techniques:

- We ask that EU regulators confirm that the products of genome editing, when they do not contain DNA from an unrelated organism, do not fall within the scope of GMO legislation.

- There should be full transparency in disclosing the process used, but the aim in the EU should be to regulate the specific agricultural trait/product rather than the technology by which it is produced. It follows that new technologies would be excluded from regulation if the genetic changes they produce are similar to, or indistinguishable from, the product of conventional breeding and if no novel, product-based risk can be identified.

Animals

Research on animals is already subject to stringent regulation and it should be appreciated that genome editing brings opportunities to enhance animal health and welfare as well as to improve agricultural traits. With regard to specific applications, we recommend the following:

- Livestock breeding should also be governed by the same principle as proposed for plant breeding—to regulate the trait rather than the technology and be open and explicit about what is being done.

- With regard to the modification of animals to serve as a source for xenotransplantation, EU regulators should actively prepare for the new opportunities coming into range: this may require further discussion of the mechanism for approving medical products relating to cells and tissues, together with assessment of the implications of whether the edited donor is regarded as a GMO or not.

Gene drive to modify populations in the wild

EASAC supports the recommendations recently published by the US National Academies:

- It is essential to continue the commitment to phased research to assess the efficacy and safety of gene drives before it can be decided whether or not they will be suitable for use.
- This research must include robust risk assessment and public engagement.
- EU researchers must continue to engage with researchers and stakeholders in the countries where gene drive systems are most likely to be applied.

Micro-organisms

- Genome editing in microbes does not raise new issues for regulatory frameworks and is currently subject to the established rules for contained use and deliberate release of GMOs.
- There is a wide range of potential applications, including pharmaceuticals and other high-value chemicals, biofuels, biosensors, bioremediation and the food chain. It is important to recognise this wide range when developing EU strategy for innovation in the bioeconomy.
- Many of the policy issues for microbial genome editing research and innovation fall within the scope of what is regarded as synthetic biology and we reaffirm the general recommendations from previous EASAC work (EASAC, 2010; and discussed further in the global context on http://www.interacademy.net/File.aspx?id=23974d). These previous recommendations for synthetic biology covered issues, for example, for building research capacity and delivering training on interdisciplinary skills in higher education.
- Concerns have been raised elsewhere about the potential for genome editing research to be conducted outside regulated laboratory settings. We recommend that the Global Young Academy should assess the issues raised by the expansion of the DIY biology community.
- Concerns have also been expressed elsewhere about the potential biosecurity implications of genome editing. We recommend that the scientific community continues to inform and advise policy-makers during review of the BWC.

Human-cell genome editing

EASAC endorses the emerging conclusions from the other collective academy work (International Summit on Gene Editing and FEAM) and the initiatives by individual national member academies:

- *Basic and clinical research.* Intensive research is needed and should proceed subject to appropriate legal and ethical rules and oversight. If, in the process of research, early human embryos or germline cells undergo genome editing, the modified cells should not be used to establish a pregnancy. EASAC recognises that the decision by the European Commission not to fund research on embryos will be unlikely to change at present.
- *Clinical use: somatic gene editing.* There is need to understand the risks such as inaccurate editing and the potential benefit of each proposed genetic modification. These applications can and should be rigorously evaluated within existing and evolving regulatory frameworks for gene and cell therapy by the EMA and national agencies.
- *Clinical use: germline interventions.* These applications pose many important issues including the risks of inaccurate or incomplete editing, the difficulty of predicting harmful effects, the obligation to consider both the individual and future generations who will carry the genetic alterations, and the possibility that biological enhancements beyond prevention and treatment of disease could exacerbate social inequities or be used coercively. It would be irresponsible to proceed unless and until the relevant scientific, ethical, safety and efficacy issues have been resolved and there is broad societal consensus.

General recommendations for cross-cutting issues

- *Public engagement.* There has to be trust between scientists and the public, and, to build trust, there has to be public engagement. As observed in the previous chapters, stakeholders (such as patients, clinicians, farmers, consumers and NGOs) need to be involved in discussions about risk and benefit, and scientists need to articulate the objectives of their research, potential benefits and risk management practices adopted. This is not a special responsibility for genome researchers, as all scientists have the responsibility to be open and candid about

their work (IAP–IAC, 2012; Nuffield Council on Bioethics, 2016). There is need for additional social science and humanities research to improve public engagement strategies.

- *Enhancing global justice.* As noted previously, there may be risk of increasing inequity and tension between those who have access to the benefits of genome editing applications and those who do not, although the widespread adoption of the technique might facilitate sharing of the benefits. The scientific community must work with others on the determinants to narrow the societal gap: for example, by active knowledge transfer, collaboration between researchers worldwide, open access to tools and education, and education efforts. It is also vital for EU policy-makers to appreciate the consequences, sometimes inadvertent, of EU policy decisions on those outside the EU. There is evidence that previous decisions in the EU (for example, on GMOs) have created difficulties for scientists, farmers and politicians in developing countries (EASAC, 2013). Reforming current regulatory frameworks in the EU and creating the necessary coherence between EU domestic objectives and a development agenda on the basis of partnership and innovation is important for developing countries as well as for Europe.

Appendix 1 Working Group composition and procedures

The report was prepared by consultation with a Working Group of experts acting in an individual capacity and nominated by member academies of EASAC:

Volker ter Meulen (Chair, Germany)
Austin Burt (UK)
Baerbel Friedrich (Germany)
Goran Hermeren (Sweden, nominated by ALLEA)
Wlodzimierz Krzyzosiak (Poland)
Cecilia Leao (Portugal)
Joseph Martial (Belgium)
Bert Rima (Ireland)
Radislav Sedlacek (Czech Republic)
Bruno Studer (Switzerland)
Miikka Vikkula (Belgium, nominated by FEAM)
Kirmo Wartiovaara (Finland)
Anna Wedell (Sweden)
Detlef Weigel (Germany)
Robin Fears (secretariat, UK)

The Working Group met in June and October 2016 in Brussels, together with external guests Johannes Fritsch (Germany) and, at the first meeting Tim Sykes (Switzerland, in place of Bruno Studer), and at the second meeting with Angelika Schnieke (Germany) and Siegrid Weiland and Jeremy Bray (European Commission Scientific Advice Mechanism). EASAC thanks the Working Group members and guests for their insight, commitment and support, and thanks members of the EASAC Biosciences Steering Panel for their advice and guidance.

The draft report was subject to peer review by experts nominated by EASAC member academies.

Abbreviations

ALLEA	All European Academies
APHIS	Animal and Plant Health Inspection Service
BSE	Bovine spongiform encephalopathy
BWC	Biological and Toxin Weapons Convention
Cas	CRISPR-associated protein nuclease
CBD	Convention on Biological Diversity
CRISPR	Clustered regularly interspersed palindromic repeats
DIY	Do-It-Yourself
DNA	Deoxyribonucleic acid
EASAC	European Academies' Science Advisory Council
EGE	European Group on Ethics in Science and Technology
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FEAM	Federation of European Academies of Medicine
GM	Genetically modified
GMO	Genetically modified organism
HDR	Homology-directed repair
HIV	Human immunodeficiency virus
IAP	InterAcademy Partnership
ILAR	Institute for Laboratory Animal Research
INSERM	Institut national de la santé et de la recherche médicale
IUCN	International Union for Conservation of Nature
NGO	Non-governmental organisation
NHEJ	Non-homologous end-joining
NIH	National Institutes of Health
ODM	Oligonucleotide-directed mutagenesis
OECD	Organisation for Economic Co-operation and Development
PAM	Protospacer adjacent motif
R&D	Research and development
RNA	Ribonucleic acid
SSN	Site-specific nuclease
TALEN	Transcription activator-like effector nuclease
UNESCO	United Nations Educational Scientific and Cultural Organization
WHO	World Health Organization
ZFN	Zinc finger nuclease

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The regulation of genome-edited plants in the European Union

EASAC commentary on the statement by the German National Academy of Sciences Leopoldina, the Union of the German Academies of Sciences and Humanities, and the German Research Foundation

Introduction to new plant breeding techniques

Agriculture continues to face major challenges to deliver food and nutrition security at a time of increasing pressures from social and economic inequity and instability, population growth, climate change and the need to avoid further loss in ecosystem biodiversity. The production of more food, more sustainably, requires the development of crops that can make better use of limited resources and will contribute significantly to attaining multiple Sustainable Development Goals.

In this commentary, the European Academies' Science Advisory Council (EASAC) expresses full support for the recent statement by the German National Academy of Sciences Leopoldina, the Union of the German Academies of Sciences and Humanities together with the German Research Foundation (Leopoldina *et al*. 2019) entitled 'Towards a scientifically justified, differentiated regulation of genome edited plants in the EU', which was prepared in response to the European Court of Justice (ECJ) decision of 2018 (C-528/16). We also note the significance of the recent decision by the European Council (Council of the European Union, 2019) to ask the European Commission to clarify the status of novel genomic techniques with regard to the options to update the existing legislation.

New breeding techniques are emerging rapidly from advances in genomics research, for application in crop improvement. They enable targeted changes in the genome and they have significant potential for the sustainable intensification of agriculture, when used as part of the deployment of all available approaches to achieving food and nutrition security and building on existing good agronomic practice. Unlike chemical- or radiation-induced mutagenesis, often traditionally used for crop improvement tools, the new breeding techniques do not create multiple, unknown, unintended mutations throughout the genome. Furthermore, the products of the new breeding techniques are also unlike genetically modified organisms (GMOs) used in agriculture, in being more precisely targeted and having no foreign DNA in the end product. Advances in plant genome editing may also support other applications for the Bioeconomy in support of European competitiveness (see later).

The scientific opportunities coming into range in plant breeding, for example, to develop more climate-resilient agriculture, resistant to the increasing abiotic

and biotic stresses, have been examined previously by EASAC (for example EASAC 2017a, 2017b) and have been explored extensively in the scientific literature (for example, the recent comprehensive review by Bailey-Serres *et al*. (2019)).

ECJ decision and the German statement recommendations

In 2018, the ECJ decided that organisms obtained by the new techniques of genome editing are GMOs within the meaning of the Directive 2001/18/EC on the release of GMOs into the environment, and they are subject to the obligations in the legal framework laid down by the GMO Directive. This ECJ declaration has been controversial (see, for example, Holme *et al*. 2019) and the background to this judgement with implications for EU science, innovation and regulation have been discussed in detail in the scientific and policy communities, for example the Group of Chief Scientific Advisers to the European Commission (2018). Their GCSA Opinion observed that new scientific knowledge has made the GMO Directive no longer fit for purpose, that the current approach does not properly respect the motivation behind the precautionary principle for ensuring product safety, and that the regulatory framework should put the emphasis on the features of the end product rather than on the production technique.

The recent German institutions' statement provides detailed assessment of the history of molecular breeding methods in agriculture, of the current research and innovation regulatory approaches used worldwide, with particular regard, for example, to issues for safety assessment and for intellectual property protection. The German statement also examines the consequences, particularly for world trade, arising from lack of consistency in regulatory approaches and the problems for product verifiability. In response to the ECJ decision, Leopoldina *et al*. (2019) propose a range of coordinated recommendations to reform EU genetic engineering law that would take account of science-based criteria in the approval process. These reforms require concomitant action to strengthen science and competitiveness in the EU (Box 1).

These recent recommendations that include concrete textual suggestions for the amendment of EU genetic engineering law are consistent with messages emerging

Box 1 Summary of recommendations from Leopoldina *et al*. (2019)

The first step is to amend EU genetic engineering legislation to include revising the GMO definition, or the associated exemptions, in order to exempt genome-edited organisms from the scope of the legislation if (1) no foreign genetic information is inserted and/or (2) if there is a combination of genetic material that could also result naturally or through traditional breeding methods.

Beyond the short-term amendment of current genetic engineering legislation, a second step should comprise developing a fundamentally new legal framework that is detached from the previous process-based regulatory approach. The new, science-based, legal framework must link the requirements of authorisation and registration to the resulting traits.

To ensure continuing development of the science base and responsible innovation in agriculture, it is also important for the European Commission and Member States to do the following.

Make field trials of new crop varieties practicable again as quickly as possible.

Support public engagement about new breeding methods, to take account of, and inform, consumer views.

Enable freedom of choice by consumers, using consistent labelling rules.

Provide broader support for responsible innovation in agriculture, e.g. by public funding of research on the health, environmental, economic, ethical and societal consequences of products and application scenarios of new molecular breeding methods. Support for innovation must also ensure that the precautionary principle is not linked to speculative risks but rather applied in the context of potential benefit-risk considerations and the risk of doing nothing.

Increase market competition by targeted incentives with particular regard to small and medium-sized enterprises currently deterred by high bureaucratic and cost obstacles.

Source: Leopoldina *et al*. (2019) with summarising by EASAC of original text on recommendations.

from EASAC work during the past two decades (EASAC 2004, 2011, 2013, 2015, 2017a, 2017b, 2018) and, indeed, with other international policy development initiatives. In addition to the international examples that the German statement cites for different regulatory approaches outside the EU (and the likelihood of increasing divergence) can be added the example of Australia and New Zealand. There, very recent recommendations from the Food Standards Authority (2019) include a proposal to revise and modernise definitions in the Code for food produced using gene technology, to ensure that new breeding techniques are regulated in a manner commensurate with the risk that they pose.

The development of strategic options for the EU has to reflect the increased knowledge derived from an ever-faster pace of science together with the accumulating experience worldwide on the use of modern molecular methods to understand plant biology. Significant opportunities are described in the German statement, including genome-edited crops already marketable elsewhere with benefits for nutrition and productive, low-pesticide and resource-conserving agriculture. In addition, there is collective need to do more to understand the genetic diversity existing naturally within a species. Although the core genome is shared by all varieties within a species, individual varieties will differ in other genes such that there may well be more, and more significant, differences between two conventional varieties than between a conventional variety and its edited counterpart.

In this brief commentary, EASAC endorses the recommendations summarised in Box 1 and takes this opportunity to update and reiterate some of our previous messages.

Global implications

It is crucially important to take account of the changing world as well as scientific advances when reflecting on policy options. EU reforms in the regulation of plant breeding are urgently needed if the objectives for EU innovation are to be met, including those for the Common Agricultural Policy, the Green Deal, and the Bioeconomy. It must also be appreciated that EU policy decisions have very significant implications elsewhere in the world. In the past, for example, the EU over-regulation of GMOs had negative impact on science and innovation in developing countries who feared for their export markets and who had been inclined to look to the EU to express leadership in research and development. This EU deterrent to innovation in developing countries can be perceived as undermining EU development policies aiming to build international collaboration in science and technology. These problems for food and nutrition security and sustainability in the rest of the world created by EU decisions are compounded by the EU exporting its lack of agricultural sustainability (EASAC, 2013, 2017b), partly in consequence of not employing on its territory all available technologies for sustainable intensification.

Given the escalating, shared, problems associated for example, with climate change, it is vital that EU actions take account of our responsibilities in the global context and that we do not repeat our past mistakes in failing to capitalise on advances in the biosciences.

Addressing policy disconnects

In addition to the disconnect noted above between EU development policy objectives for science and technology collaboration, and the consequences of over-regulated and inconsistent GMO policy, EASAC has previously emphasised (EASAC 2013, 2018) other contradictions which undermine the EU desire for coherent strategy to address major societal challenges. These contradictions include those between:

- The European Commission's leadership in support for science *and* those regulatory impediments to innovation that are felt most strongly in academia and the small and medium-sized enterprises. EU citizens are poorly served if their contribution to the funding for cutting edge science does not lead to them benefitting from the knowledge generated.

- The productivity goals for EU climate-resilient agriculture (for planetary health) that also protects human health *and* the practical difficulties in using all appropriate technologies to respond to climate change.

- The environmental goals for EU agriculture to reduce the external application of chemicals (fertilisers, pesticides and herbicides) *and* the impediments to identifying and breeding new crop varieties that require less application of such chemicals. The United Nations Year of International Plant Health in 2020 is particularly relevant for reaffirming the contribution that improved plant breeding can make to plant and planetary health. The EU could provide leadership globally to reduce the use of pesticides and fertilisers as well as mitigating the impact of environmental change on food sustainability.

- The current EU practice of importing genetically modified food and feed that is not approved for cultivation on EU land: the consequences of this also run counter to EU aspirations to limit 'food miles'. Unless the EU response to climate change includes developing climate-resilient agriculture, it can be foreseen that the EU will require to import more food and feed, and an increasing proportion

of this is likely to be from the use of new breeding techniques elsewhere in the world.

Ethical issues and proportionality

EASAC has previously highlighted (EASAC, 2017a) how there is a moral obligation to fight disease and relieve suffering. To the extent that genome editing technologies provide useful tools to achieve such purposes, there is an opportunity cost in using them too late or not at all, particularly if they are safer, more effective and cheaper than alternative technologies.

Ethical problems are raised by conflicting values, by interests that pull in different directions. If and when interests or values clash (when certain values or interests can only be achieved at the expense of others), principles are available that can guide the decision-making. Two such principles with implications for the particular issue of plant breeding are the precautionary principle and the principle of proportionality.

If the precautionary principle implies 'do nothing if there are unknown risks', this will halt progress, and doing nothing also entails risks (EASAC, 2015). But if the principle means only 'act with caution', it has to be made clear what this means in practice. Safety is obviously important, but so are the benefits. One possibility is to say that it suggests: 'act according to the principle of proportionality'. The precautionary principle, if strictly interpreted, requires work to stop if there are uncertainties about the risks involved, and it places the burden of proof of safety on those who want to promote a change. But the principle of proportionality is more open, in its four conditions (Hermeren, 2012), which at all times can be discussed, assessed, argued for and applied in the light of the present evidence. Decisions can then be taken, which can be changed as the scientific evidence and value landscape changes:

1. *Importance of objective* — the intended goal, theoretical or practical, should be important.

2. *Relevance of means* — the means should bring about or at least help to achieve the goal.

3. *Most favourable option* — there is no other less controversial or risky means to achieve the goal(s).

4. *Non-excessiveness* — the means used should not be excessive in relation to the intended goal, which requires analysis, argument and interpretation.

This suggests an approach, termed stewardship, implying or encouraging an ongoing overview of processes in the light of changing evidence and values within restrictions imposed for example by respect for human rights. However, experience of GMO Panel members of the European Food Safety Authority (Casacuberta and Puigdomenech, 2018) indicates that there has been a reduction in the flexibility of the risk assessment procedures for GMO crop applications, even while the evidence base worldwide (including the substantial evidence for lack of harm) has accumulated. From this perspective, there is pressing need to make use of the proportionality principle when introducing reform to strengthen the use of scientific evidence and tackle future uncertainties.

The issues are receiving considerable attention in Member States and the European Commission. For example, the Opinion published in France by the Ethics Committee of INRA (2016) provided an important perspective on the link between agricultural and environmental considerations. The European Group on Ethics in Science and New Technology recently organised a roundtable on gene editing, including plant applications (EGE, 2019) and discussion was clearly polarised. It continues to be important to take the range of public perceptions into account, against a background of contested knowledge, when formulating policy in this area (see next section) and the forthcoming Opinion to be published by the EGE will be a significant contribution to catalysing further discussion.

Public opinion

Public discussion about GMO crops tended to become a proxy for other much-needed discussion about food security and safety, farming systems, fair competition, social justice, the economic power of multi-national companies and the apparent conflict between intellectual property protection and benefit sharing (EASAC, 2013). If the differing public values are to be better understood as part of attempts to reconcile them and if we wish to avoid repeating the same mistakes in public engagement on genome editing, then the multiple determinants of each controversy need to be made more transparent. It is also vitally important to learn lessons from history: an inadvertent consequence of EU GMO legislation and the high costs inherent in seeking regulatory approval has increased multi-national company monopoly in the commercial agricultural model. The Leopoldina *et al*. (2019) statement highlights the importance of increasing market competition by targeting incentives for smaller companies. Competition might also be enhanced by further exploration of the options for protecting intellectual property rights to take account of the issues for maintaining co-existence between breeder's rights and patents (EASAC, 2013). Plant Breeders Rights provides a well tried and tested system whereby breeders can secure financial returns on the release of a successful variety without jeopardising future societal benefits to be derived by even further genetic improvement that might be achieved by others.

It is beyond the scope of this short commentary to discuss in detail the varying public perceptions on genome editing in plants but it is worth mentioning that public surveys in the UK, commissioned on behalf of the Royal Society (van Mil *et al*. 2017)[1] demonstrate significant public support. For example, there was support for the use of genome editing to prevent crop damage by fungal diseases (77% of the group surveyed), to make crops more nutritious as a way of supplementing poor diets (70%) and in the biosynthesis of cheaper medicines (69%). Of course, these high approval ratings are expressed subject to necessary conditions: the use of genome editing as part of a package of solutions, with equitable access, no harm to the environment, publicly accessible information, effective regulation and ethical guidance in place.

It may be inferred that public opinion in many EU Member States is willing to consider the benefits of crop genome editing judging from the initiative of 14 countries, led by the Netherlands and Estonia. The advice from the Dutch agricultural ministry and others, following the ECJ ruling calls for the reform of GMO laws with regard to new breeding techniques, also observing that organisms obtained by mutagenesis have been used in farming for many years and have a long safety record[2]. As emphasised recently by former EU Health Commissioner Vytenis Andriukaitis[3], there is need for continuing dialogue with all sectors in society in the necessary rethinking of the cumbersome policy that currently deters new breeding techniques, '*yet this talk should not be at the expense of science and innovation*'. In the view of EASAC, dialogue does not need to continue to be primarily about the value of genome editing technologies, or GMOs, because this value is already demonstrable. Rather we need to debate about how the value of these technologies can be obtained for the EU and how the EU can contribute to achieving global food and nutrition security.

Other applications of new plant breeding techniques

Agricultural biotechnology, including genome editing, has potential to contribute to societal objectives in pursuit of the Bioeconomy in other ways in addition to food and nutrition security, for example in the search for the next generation bioenergy and in the biosynthesis of medicinal products, other high value chemicals and the building blocks for renewable industrial synthesis (see, for example, Tatsis and O'Connor, 2016; Liu *et al*. 2017; Mortimer, 2019; Najera *et al*. 2019).

Summary of EASAC messages

EASAC endorses the Leopoldina *et al*. (2019) recommendations and now also reiterates our core recommendations on new breeding techniques from the previous EASAC work (2015, 2018):

- Products of new technologies and their use, rather than the technology itself, should be evaluated according to the scientific evidence base.
- The potential costs of not using a new technology, or being slow in adoption, must be acknowledged. There is no time to lose in resolving the problems for food and nutrition security in Europe.
- If a product of genome editing does not contain foreign DNA, it should not fall within the scope of EU legislation on GMOs.
- More broadly, there should be full transparency in disclosing the process used and the EU should seek to regulate the trait and/or product rather than the technology used in generating that product. That is, when considering safety issues, the focus should be on assessing whether the novel attributes of the plant might represent a risk to the environment or human health, irrespective of the breeding technique employed.
- The European Commission should continue to commit to supporting fundamental research in plant sciences to provide the tools and other resources for future innovation in plant breeding and farming practices.
- There is also continuing need for wide-ranging engagement to discuss critical, including ethical, issues to build trust between scientists and the public.

EASAC directs our messages to the European Commission, Council and Parliament and to policy makers in the Member States. The request by the European Council to the European Commission to clarify options to update the existing legislation might be interpreted minimally by some only as an examination of how to deal with products where the mode of molecular change cannot be detected, but in our view, this would then be a missed opportunity. The request from the Member States should rather be viewed as an invitation to the European Commission to set out

[1] This research involved use of focus groups with a broad demographic of participants plus a quantitative online survey (n = 2,000) to validate the dialogue findings.
[2] 14 EU countries call for 'unified approach' to gene editing in plants, www.euractiv.com, 24 May 2019.
[3] Andriukaitis: Europe should take lead in science-based plant innovation, www.eurativ.com, 4 December 2019.

the strategic options for EU agricultural innovation and responsibilities in the wider international context, leading to a reopening of Directive 2001/18/EC. EASAC reaffirms the importance of exploring radical reform and urges the EU Institutions to explore the options recommended by Leopoldina *et al*. (2019) and others:

- First, to revise the GMO definition/exemptions to enable the EU to capitalise on the plant breeding opportunities afforded by genome editing.
- Secondly, to develop a new legal framework to focus on traits not processes.

Reform is needed urgently: if provision is not made soon for an evidence-based flexible and proportionate regulatory framework, there is little prospect of agricultural innovation realising its potential in achieving the Sustainable Development Goal targets by 2030 or of the EU maintaining international competitiveness.

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