Meeting of the States Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction

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Genome editing, taking into consideration, as appropriate, the issues identified above

Genome editing: addressing implications for the Biological and Toxin Weapons Convention

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I. Introduction

1. Recent developments in genome editing were introduced during the 2012 to 2015 Intersessional Programme Standing Agenda Item on review of developments in the field of science and technology related to the Convention. In particular, advances in CRISPR-based technology, derived from the natural defence mechanisms of bacteria, gave it potential as a powerful genomic engineering tool also applicable in more complex organisms, including plants, insects, animals and humans. Its increasing affordability, accessibility, precision and rapidity enhanced this potential. However, the rapid emergence and advancement of this field meant that the implications for the Convention, particularly the security implications, were uncertain and difficult to predict.

2. Detailed technical descriptions of genome editing have been provided in presentations and Working Papers at previous BTWC meetings[1] and will also be covered in contributions to this MX2. This Working Paper focusses instead on the potential

1 For example: Presentation by Switzerland to 2015 BTWC Meeting of Experts: https://www.unog.ch/80256EDD006B8954/(httpAssets)/A60F7B2106175E24C1257E9F0065DDEF/$file/Swiss_presentation_BWC_MX_2015_S&T-CRISPR_INC.pdf. New scientific and technological developments relevant to the Convention: Some examples. Submitted by the United States of America (BWC/CONF.VIII/PC/WP.18)

consequences of advances in this field for the elements specified in the MX2 agenda, which are: enhanced implementation of the Convention; identification of potential benefits and risks; biological risk assessment and management; codes of conduct and biosecurity education. In particular, it aims to identify some topics and questions to stimulate expert discussions in MX2 on the opportunities and challenges emerging, and on the actions that States Parties could consider, individually and collectively, to address them.

II. Potential benefits and risks

3. Genome editing has the potential to provide benefits across an increasing number of areas, including in human health, agriculture and the environment. There could also be beneficial outcomes of relevance to implementation of the Convention, for example, in providing support or assistance in the response to the effects of a violation of the Convention under Article VII, and in development and application of scientific discoveries to the prevention of infectious disease under Article X. CRISPR technology is already being developed to prevent and treat disease in humans, to modify plants to deal with the impacts of climate change and plant pathogens, and to halt the spread of viruses in animal populations. It can also be used to edit germline cells in embryos, introducing genetic changes that will be passed on to future generations and which could have potential in the treatment of genetic disorders. Some specific examples of beneficial genome editing applications given in a recent Royal Society Conference Report[2] include:

- conferring resistance to porcine reproductive and respiratory disease virus in pigs and to the infectious pancreatic necrosis virus in Atlantic salmon;
- targeted mutagenesis to prevent rice blast disease;[3]
- creation of improved cellular and animal models of disease to understand disease pathways, identify and validate novel drug targets and test the efficacy of new medicines;
- targeting of the genes involved in the symbiosis signalling pathway in barley to help understand their function. This may allow engineering of the pathway for cereal recognition of nitrogen-fixing bacteria, and support the development of nitrogen-fixing cereals, which could play an important role in global food sustainability.

4. The Royal Society Conference Report also addressed the technical, regulatory and ethical challenges associated with the wider adoption of genome editing technology. The broader debate on the socio-economic implications of genome editing has tended to focus on the key ethical, moral and public perception aspects, though there has been some consideration of potential security concerns. In October 2017, the InterAcademy Partnership (IAP) convened an international workshop to assess the security implications of genome editing technology. Its major goal was to enable members of the research, security and policy communities, with wide geographical representation, to discuss potential benefits, security implications associated with intended misuse, and what might be done to prevent or mitigate potential harm.[4] Discussions focussed on specific applications of

[2] The CRISPR revolution: changing life: Conference report. Held on 7 March 2018 https://royalsociety.org/~/media/events/2018/03/crispr-revolution-tof/TOF-crispr-revolution-report.pdf?la=en-GB

[3] Rice blast disease has been weaponised as a BW agent in the past.

[4] Assessing the Security Implications of Genome Editing Technology. Report of an international workshop, Herrenhausen, Germany 11-13 October 2017. Convened by the IAP, the European Academies' Sciences Advisory Council (EASAC), the US National Academies of Science,

genome editing, including: human cell editing; editing in agriculture (plants and animals); gene drive applications; and microbial applications. Participants identified beneficial applications similar to those mentioned in the Royal Society report; additional examples included:

- developing gene drives, for example, to control insect vectors of diseases such as malaria;
- application in transgenic cattle for increased resistance to tuberculosis;
- development of screens for biological processes or disease;
- increased understanding of CRISPR functionality in bacteria revealing new opportunities to tackle pathogens, including the major therapeutic goal to avoid development of antimicrobial resistance.

5. Potential security concerns, specifically intentional misuse, were explored taking account of developments in the specific applications. Issues included:

- Human cell editing concerns such as: influencing future human generations; misuse potential for 'off-label' use, for example using a medical product for a muscle disorder for enhancement of military capabilities ('super soldiers'); risk of genome editing viral vectors reaching unintended recipients;
- Microbial applications have the potential for misuse to construct or alter pathogens suitable for weaponisation[5]; this would be of concern in both human health and agriculture;
- Gene drive applications could potentially be misused to create threats to human health (e.g., by increasing the transmission of infectious disease by insect vectors) and agriculture (e.g., by increasing insect pests and plant damage).

6. In assessing both potential benefits and risks, it is also important to consider the present and future limitations of the technology and what barriers would have to be overcome to address the challenges. Some examples of limitations include:

- unwanted off target effects which can confound research experiments and present problems for therapeutic applications; development of more specific variants of CRISPR system enzymes could minimise these effects;
- pre-existing immune responses in humans to proteins in the CRISPR-based technology; this may hinder use to treat disease and could cause significant toxicity to patients; utilisation of alternative enzyme variants may address this;
- delivery to the target population based on viral-vector systems, which have limitations on size of insert, efficacy and specificity; new approaches being explored include utilisation of gold nanoparticles complexes to improve delivery.

III. Biological risk assessment and management

7. The workshop and its report were intended as the first steps in catalysing and supporting further debate on the security implications of genome editing technology, thus

Engineering and Medicine (NASEM), and the German National Academy of Sciences Leopoldina. http://www.interacademies.org/Publications/43251.aspx

[5] The relevance of the categories of concern identified in the Fink Report was highlighted: National Research Council. 2004. Biotechnology Research in an Age of Terrorism. Washington, DC: The National Academies Press. https://doi.org/10.17226/10827

general observations made may now serve as a basis for further assessments. Questions that were debated and which emerged during the workshop's discussions are relevant to our work in MX2, particularly in determining if and what advances in the field might be of concern as a risk to the object and purpose of the Convention, and what strategies might be appropriate to address such risks. Some questions that may help structure our deliberations are set out below.

8. What are we concerned about?

- Which particular developments are most relevant and likely to have impact in the near future?
- What is the feasibility for misuse? Is the technology readily accessible and usable for such activities? What are the limitations?
- What range of activities need to be considered, e.g., direct use of CRISPR technology to cause harmful effects in humans, animals or plants; use of the products of genome editing, such as constructed or altered pathogens, to cause disease; indirect approaches, for example, based on the lack of traceability of CRISPR editing in the product that may challenge microbial forensics?
- Is its application dependent on the simultaneous development of other technologies, such as production and delivery systems? (Applies in both benefit and risk contexts).
- What are the considerations for intangible technology, such as tacit knowledge and the accessibility of the knowledge base for potential misuse?
- Is there anything unique about genome editing in the security context, or can it be considered as an extension of other genetic technologies and addressed in broader considerations of emerging technologies?

9. How should we assess the risks?

- In the absence of broadly accepted norms, how should we assess potential concerns and ensure that benefits and risks are balanced? What regulatory and/ or guidance frameworks are available to consider in harmonisation of approaches and best practices? Could we consider a set of guiding principles? Would approaches need to be specific for genome editing/genetic technologies, or could they be wider-based to allow assessment of risks for all relevant emerging technologies?
- Are there relevant case studies on CRISPR-based experiments to utilise in risk assessment? Would case studies from the past or present involving other genetic technologies provide useful lessons? (For example, much-debated cases such as the synthesis of polio virus, construction of the 1918 influenza virus, 'gain of function' avian influenza experiments and construction of the horsepox virus. A recent publication on 'gain of function' analysis of Yersinia pestis, the causative agent of plague may also be of interest.[6])
- Who should be involved in predicting the implications? How do we achieve an optimal balance between scientific, policy, ethical, environmental and security concerns? How do we reflect different national interests and capture a broad range of voices globally to clarify perceived risks and weigh the benefits and risks ?

[6] Palace, S.G. et al. Gain of Function Analysis Reveals Important Virulence Roles for the *Yersinia pestis* Type III Secretion System Effextors YopJ, YopT and YpkA. (2018) Infection and Immunity Accepted Manuscript Posted Online 11 June 2018. Infect. Immun. doi:10.1128/IAI.00318-18.

- Are risk assessments on other aspects, such as safety and ethics, of relevance to implementation of the BTWC? (For example, biosafety assessments may be relevant for implementation of Article IV). How should we interact and keep abreast of discussions and outcomes in other settings?

10. How should we manage the risks?

- What are the primary legal, regulatory and policy measures that could be applied to address and mitigate the potential security risks? Which approaches from the range of governance measures identified (including legislation, regulations, guidelines, standards, funder reviews and oversight, codes of conduct, education, and self-governance) would be appropriate and in what combinations?
- How far can these be harmonised? Is there a risk from conflict between different governance systems (e.g. in different sectors and by other bodies)?
- Are there any technical measures that could be applied to reduce the risks? (For example: safeguarding gene drives to reduce off-target effects and inhibiting spread; increasing efficiency in delivery of viral vectors to ensure specific targeting; development of countermeasures to reverse genome editing or enable detection.)
- Would it be useful to develop guiding principles for balancing the benefits of scientific research with the responsibility to prohibit and prevent the development and acquisition of biological weapons?
- On what aspects should governance measures focus? Generally it was considered that the focus should be on regulating the products of genome editing rather than the technology itself – is this the case for all measures?
- When should decisions on governance be made and at what stage of technology readiness (from initial research through to product) should they be applied? How can we ensure that proportionate and adaptive governance measures are considered?7 Are there existing measures that adequately cover, or could be extended to cover, genome editing advances?
- Who needs to be involved in decision-making on governance measures? Who would provide advice to policy makers? What communities have the responsibility to ensure the responsible development of the technology?

IV. Codes of conduct and biosecurity education

11. Codes of conduct and education are amongst the potential measures considered in biological risk management, and would be included in discussions on this element. However, the workshop report includes some relevant feedback from participants. It recognised a need to create a culture of responsibility encompassing researchers, funders, publishers and others, and opportunities to integrate education on security into wider initiatives on responsible research, embedding it in career structures. Ongoing training and education could help ensure that scientists understand the possible dual-use nature of genome editing work. Fostering mentorship was proposed as a core part of developing

[7] See: The CRISPR revolution: changing life: Conference report. Held on 7 March 2018 https://royalsociety.org/~/media/events/2018/03/crispr-revolution-tof/TOF-crispr-revolution-report.pdf?la=en-GB and: Tait, J., Banda, G. and Watkins, A. (2017) Proportionate and Adaptive Governance of Innovative Technologies: a framework to guide policy and regulatory decision making. Innogen Institute Report to the British Standards Institution. https://www.innogen.ac.uk/reports/1222.

responsible conduct; for example, principal investigators should be role models for their students.

12. Codes of conduct were proposed to be a useful part of a concerted governance system. Some suggested aims were: to raise awareness and broaden discussion; give incentive for assuming responsibility for one's own research; anticipate or pre-empt regulatory requirements; and foster public confidence.

V. Conclusions

13. The workshop session on the way ahead highlighted the importance of continuing discussions on the security implications of genome editing; some of the issues could be developed to expand the scope and scale of further debate. The workshop report indicates the desirability of building on shared evidence and links formed to develop a sustainable network encompassing the scientific and security communities as a basis for extending the engagement more widely. During the workshop, it was pointed out that there would be continuing opportunities for the scientific community to engage with policy makers during meetings of the BTWC. This first Meeting of Experts on the review of developments in the field of science and technology related to the Convention presents such an opportunity - to extend the engagement and draw upon relevant expertise to help us assess the implications of genome editing for the Convention.