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

Review of Developments in the Field of Science and Technology Related to the Convention - Genome editing

Submitted by Australia

I. Overview

1. The rapid advances in genome engineering technology, in particular, the emergence of clustered, regularly interspaced, short palindromic repeat (CRISPR) has revolutionised human, animal, plant and ecosystem health. The CRISPR/Cas9 system is a site-directed nuclease that can be used for altering genetic loci through insertions, deletions and point mutations in virtually any organism, creating changes that fall into different categories of genome engineering. The insertion of foreign DNA generates genetically modified organisms (GMOs), whereas site-directed mutations including deletions and small base pair changes are classified as gene editing. Gene editing outcomes can be generated with a site-directed nuclease alone or in combination with a DNA repair template. Rapid advances over recent years have resulted in improved efficiency, relatively high precision and low cost, making this technology now a mainstream method, accessible to academic, government or industry laboratories and potentially even civilian run laboratories. These characteristics have also led to some concern over how quickly applications for beneficial or harmful uses will be developed and spread.

2. BWC MX2 on “Review of Developments in the Field of Science and Technology Related to the Convention” offers the opportunity to discuss emerging technologies and consider potential risks and benefits relevant to the Convention. The current paper provides an overview of the capabilities and regulations associated with this technology in Australia and the implications for Australia and the Indo-Pacific region. Increased transparency and sharing of information on the experiences of States Parties in managing the risks associated with gene editing, including through regulation, is a useful way to strengthen the BWC and keep it relevant to contemporary challenges.

II. Accessibility of gene editing: what are the risks and rewards?

3. Methods for genome editing are readily available in scientific papers and on the internet. Additionally, CRISPR/Cas9 kits can be ordered online relatively cheaply by anyone, regardless of their training or expertise. This ready availability has accelerated progress and allowed the technology to be used across a variety of applications. The use of genome engineering to make disease vectors less effective at carrying pathogens such as malaria, developing novel human therapeutics, improving disease resilience of host species to pathogens, and for controlling invasive species are among the benefits promised by this technology.

4. The availability of tools and information to edit the genomes of many different organisms ranging from cattle[(1)] to vaccinia virus[(2)] has also led to concerns over misuse of such information and its potential as a biosecurity threat. In the past inadvertent discoveries have also led to the dissemination of information that could be used for harm. One example is the unintentional development of a lethal mousepox virus using standard genetic modification techniques to insert the gene for interleukin 4 (IL4) into the mousepox viral genome, an insertion which was intended to be used to induce infertility in mice. Instead, the altered virus was lethal in naturally resistant mice, and mice that had been vaccinated against mousepox. When the authors published their findings, critics were concerned that this information could be used by would-be terrorists as a new way of making biological weapons[(3,4)]. Beyond micro-organisms, there is also the possibility of engineering vectors such as mosquitoes that spread pathogens such as Zika or Dengue viruses more effectively.

5. While risks of misuse of this powerful new technology exist, it should be noted that although new site-directed nuclease such as CRISPR/Cas9 are accessible and easier to use than former methods, to use any genome engineering tools in conjunction with microorganisms one must still have access to the live microorganisms and the capacity to grow those microorganisms in culture and deliver the genome engineering tools to those cells. In multicellular eukaryotic organisms these tools are even harder to use on an organismal level as one must have access to either gametes, stem cells, or embryos to make germ line transmissible changes to the genome. Thus, to effectively undertake a gene editing project in any organism would require access to that organism, training in laboratory techniques, and access to basic laboratory equipment.

III. Regulations governing gene editing technology in Australia

6. Australia's governing body that regulates all genetically modified organisms, the Office of Gene Technology and Research (OGTR) within the Australian Government Department of Health is responsible for administering the Gene Technology Act 2000 and corresponding state and territory laws. The OGTR oversees all work involving gene technology performed in Australia, including the development of policy guidelines in relation to genetically modified organisms. In the 2001 Explanatory Statement to the Gene Technology Regulations, the scope of gene technology as defined by the scheme states that any process that involves moving and rearranging genes between species is considered gene technology and results in GMOs, whereas techniques which mimic natural processes and work through natural mechanisms do not result in GMOs. As such, organisms resulting from technologies such as chemical and radiation induced mutagenesis are not considered to be GMOs for the purposes of the legislation because the process mimics natural mutation processes[(5)].

7. The emergence of new tools including site-directed nucleases such as CRISPR/Cas9 triggered a technical review of the gene technology regulations in Australia which began in 2016[(6)]. In early 2018, the OGTR set forth recommendations based on the technical review proposing that organisms modified using site-directed nucleases without DNA templates to

guide genome repair should not be regulated as GMOs, as the site-directed nucleases only cleave DNA and all resulting mutations at the cleavage site are generated through natural cellular processes. Any organisms generated using site-directed nucleases in conjunction with DNA templates to direct repair of the DNA cleavage will be regulated, as the use of DNA repair templates constitutes gene technology[(7)].

8. While organisms made using only site-directed nucleases would not be regulated under this proposal by the OGTR, there are currently no domestic sources of CRISPR/Cas9 plasmids, mRNA, or protein, thus all non-laboratory organisms (as classified by the Australian Department of Agriculture and Water Resources)[(8)] made with these reagents would still fall under quarantine regulations regarding the *in vivo* use of imported biologics (importing biological products for use in non-laboratory animals). As many other countries are also grappling with how they will regulate organisms made using site-directed nucleases, it will be useful to hear the experiences of other States Parties during the MX, as such dialogue helps us to share best practice, and avoid mistakes.

9. Other jurisdictions are also currently deciding how they will regulate organisms made using site-directed nucleases. Overall, the international regulatory landscape surrounding site-directed nucleases like CRISPR/Cas9 remains very fragmented, with a significant focus on the regulation of commercially relevant agricultural species, human therapeutics, and microorganisms used in industrial processes. As is the case with more traditional techniques used for genetic modification, the burden of closely monitoring the use of these technologies in harmful microorganisms falls to separate institutions, be they scientific, medical, academic or government. Institutions have an ethical and legal responsibility to ensure that biosecurity standards are maintained for all work taking place at the institution and for instilling a positive and transparent culture in the workplace.

10. All organisations in Australia undertaking dealings with GMOs undergo accreditation to assess whether they have the resources and the internal processes in place to enable effective oversight of work with GMOs. This includes access to an appropriately constituted Institutional Biosafety Committee which provides on-site scrutiny of low-risk contained dealings through independent assessment to ensure compliance with legislative requirements. All staff undertaking work with GMOs are also required to undertake training to ensure they are aware of the regulations and requirements. Despite these requirements, there will always be the risk that staff members who have access to harmful microorganisms and the expertise to use genome engineering techniques on them may use this material and their expertise for harmful purposes, even if these activities are illegal. Strong institutional oversight of projects, restricted access to harmful microorganisms, and clear reporting mechanisms for documenting the possible risks associated with these types of projects are ways that institutions can prevent either unintentional or malicious misuse by staff of the materials and expertise they have been entrusted with.

IV. Facilities for high containment and Resources for Capability building

11. The Australian Animal Health Laboratory in Geelong, Victoria is the largest high containment lab in the Southern hemisphere with laboratory and animal capacity to work with pathogens up to the highest level of containment, biosecurity level 4 (BSL4). The lab also has significant expertise in genome engineering and diagnostics. To this end, genome engineering is being used for a variety of applications, including projects involving editing the engineering of animals to confer improved disease resistance, control invasive species, and in mosquitoes to decrease disease transmission.

12. Although the high containment lab was originally built to contain dangerous pathogens, it also provides the opportunity to contain genetically modified or gene edited

organisms, including animals, microorganisms and insect vectors of disease without the risk of accidental release. In the event of a natural incursion or intentional release of a harmful agent, this laboratory is well placed in the Indo-Pacific region to perform diagnostics and coordinate a response plan. In addition, this laboratory is an ideal place to test potential therapeutics against novel pathogens using animal models at high biocontainment.

13. In addition to laboratory capacity in Australia, training and capacity building in other countries in the Indo-Pacific region is critical for disease preparedness against outbreaks due to naturally occurring and intentionally released organisms. To this end, the Australian Government launched the A$300 million, five year Indo-Pacific Health Security Initiative on 8 October, 2017. The program is focused on building capacity in emerging infectious diseases in the Indo-Pacific region, including supporting action at the country or subregional level to strengthen regional capacity to prevent, detect and respond to emerging and re-emerging infectious disease threats with the potential to cause social and economic harms on a national, regional or global scale. This will include training of scientists and lab workers in biosafety, biosecurity and laboratory diagnostics. This capability has the potential to extend to the ability to respond to and detect a threat posed by a deliberately released, modified microorganism.

V. Synthetic biology – the next biothreat?

14. Synthetic biology is the ability to design and build artificial biological systems for research, engineering and medical applications[(9)]. Beyond the risks posed by genome editing, the issues in the future may have more to do with the synthesis of new pathogens rather than editing known pathogens to make them more virulent. Even if the agent is restricted, the DNA is not. The most likely applications for synthetic biology could involve recreation of known pathogens such as the highly virulent 1918 Spanish flu whose sequence is publicly available[(10)]. Another example which has raised recent concern is the publication of a method to reconstruct horsepox virus by gene synthesis[(11)]. Given the close relationship between horsepox and smallpox virus, implications for the transfer of the techniques used for horsepox have clear implications for public health and biosecurity if they were applied to the synthesis of the smallpox virus.

15. A number of companies provide DNA synthesis services, allowing a client to order synthesised DNA material as short oligonucleotides of less than 100 nucleotides or DNA sequences of between 200-3000 nucleotides in length. Although there are a number of ways of producing a synthetic viral genome using either short oligonucleotides or longer DNA sequences, the technical challenges associated with creating a functional genome are considerable. As with genome engineering, the extensive knowledge and technical expertise required for synthetic biology applications may prevent its misuse, at least in the short term. Although the risk remains small at this stage, the consequences of the misuse of synthetic biology are considerable. Managing the risks by careful regulation of materials, including the distribution of synthetic DNA and methods for generating novel organisms will be assisted by international consideration and cooperation in the BWC framework. The applications of synthetic biology as they relate to the creation of biological weapons is an important issue that should be considered by the Biological Weapons Convention as a potential topic for the 2019 meeting.

VI. Conclusions

16. The rapid advancement of genome engineering and synthetic biology have generated considerable concern that their misuse could create a new generation of biological weapons. The technical expertise required for genome engineering places it beyond the reach of most terrorist groups. However, regulation of GMOs, quarantined biologics, and harmful

microorganisms, by Australian Government agencies such as the Office of the Gene Technology Regulator and Department of Agriculture and Water Resources play an important part in ensuring the safe use of this technology. Institutions, be they scientific, medical, academic or government, also have an important role to play in ensuring that biosecurity is maintained and that employees who have the technical expertise to use genome engineering or synthetic biology and access to biological agents do not use them for harm. Concerns over genome engineering and synthetic biology can also be addressed to some extent by improvements in our capacity to respond to emerging infectious diseases. To this end, Australia's existing capabilities in emerging infectious diseases and the capacity building activities of programs such as Australia's Indo-Pacific Centre for Health Security are important for maintaining and building the capacity to respond to infectious disease outbreaks that occur either naturally or due to intentionally released, modified organisms. Gene editing is a useful, relevant topic for BWC experts to consider, and MX2 will provide an important opportunity to start the discussion. It will be equally valuable to continue the dialogue building on the meeting in August 2018.

VII. References

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Footnote

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