SCIENTIFIC AND TECHNOLOGICAL DEVELOPMENTS RELEVENT TOTHE BIOLOGICAL WEAPONS CONVENTION

Submitted by Australia

1. Australia provides the following information to the Biological Weapons Convention (BWC) Secretariat, UN DDA, Geneva, on scientific and technological developments relevant to the Convention, in accordance with paragraph 22(c) of BWC/CONF.VI/PC/2.

2. Australia considers that the key scientific and technical development relevant to the BWC that has occurred since its entry into force is the **widespread application of modern genetic techniques**. These techniques have enabled the rapid and relatively inexpensive identification, characterisation, mapping, manipulation and synthesis of genes and short strands of genetic material. The developments have potential to be applied for beneficial peaceful purposes, consistent with the objectives of the BWC, but also may be applied maliciously, in breach of the Convention (i.e. they pose a 'dual use' dilemma).

3. Australia suggests that developments in the life sciences relating to the following research disciplines are also relevant to the BWC, either because the discipline has matured since the last BWC review conference and/or because recent technical advances have increased the ease with which the discipline may be applied:

(i) Synthetic biology (a discipline combining biology and engineering that seeks to design and build novel biological systems)
(ii) Genomics (the branch of genetics that studies organisms in terms of their genomes, i.e. their full genetic sequence)
(iii) Proteomics (the branch of genetics that studies the full set of proteins encoded by a genome); and
(iv) Nanotechnology (the branch of engineering that enables the manipulation of individual molecules including, potentially, those that may be derived biologically).

4. We note that advances in these disciplines have been possible because of modern genetics and the application of associated techniques. In this context, Australia emphasises the relevance of key experiments, outlined in Tables 1 and 2, that pose a dual use dilemma[1]. Table 1 provides an overview of experiments relevant to the BWC that are likely to involve modern genetic techniques. Table 2 outlines additional experiments relevant to the BWC that would not, necessarily, employ these techniques.

5. We note that, while many of these experiments — especially those in Table 1 — are theoretically possible and/or have been conducted and published in the peer-reviewed scientific literature, they are currently technically challenging, even for well-funded and coordinated research programs. Annex I outlines some of these challenges with respect to synthesising pathogenic organisms *de novo*, as occurred in 2002 with the polio virus — an experiment and

[1] Information in Tables 1 and 2 is drawn from a draft report by the Centre for Applied Philosophy and Public Ethics (CAPPE; see http://www.cappe.edu.au/): Miller, S. *et al.* (2006) "*Ethical and Philosophical Consideration of the Dual-Use Dilemma in the Biological Sciences"*

publication[2] that alerted the international community to the relevance of rapid biotechnological developments to the BWC and the threat of bioterrorism.

Table 1. Experiments likely to involve modern genetic techniques relevant to the BWC

Experiment/technique	Relevance to BWC – the dual use dilemma
Rendering a vaccine ineffective	• It is important to know whether/how vaccines can be made ineffective, to enable their improvement or identification of alternative treatments. • Rendering a vaccine ineffective could allow the deployment of biological weapons that are unable to be treated using standard vaccination techniques.
Conferring resistance to therapeutically useful antibiotics or antiviral agents in pathogenic organisms	• Conferring antibiotic resistance may provide data that helps improve the administration of antibiotics, or be used to test the efficacy of alternative antibiotics. • The same technique could also be used to produce an 'untreatable' bioweapon that is resistant to common antibiotics.
Enhancing the virulence of a pathogen or rendering a non-pathogen virulent	• For public health reasons, it may be important to know whether and/or how the virulence of a pathogen that exists in nature can increase. • An 'enhanced' pathogen, if deployed in a biological attack, would inflict more human damage than normal.
Increasing the transmissibility of a pathogen	• For treatment and public health planning purposes, it may be important to know whether a naturally-occurring infectious disease threat could be worsened by the evolution of a pathogen into a more transmissible form. • A pathogen might be more useful as a biological weapon if it is more easily transmitted through a population.
Altering the host range of a pathogen	• It may be important to know whether a non-zoonotic disease can become, or is close to becoming, a zoonotic agent. • The use in a biological attack of an animal disease agent that has been engineered to infect humans would be devastating because people would have no immunity to the disease.
Enabling the evasion of diagnosis and/or detection by established methods	• It may be important to know whether a pathogen has the potential to mutate naturally into an undetectable form so that new diagnostic/detection techniques may be devised. • Pathogens engineered to evade diagnosis and/or detection would be well-suited for a covert biological attack, and the delay in diagnosis and subsequent treatment would increase the resulting human damage.

[2] Cello J, Paul AV, Wimmer E.Chemical synthesis of poliovirus cDNA: generation of infectious virus in the absence of natural template. Science. 2002;297(5583):1016-8

Experiment/technique	Relevance to BWC – the dual use dilemma
Undertaking genetic sequencing of pathogens	• Sequencing the genetic code of entire pathogens or specific genes of pathogens could assist in understanding the nature of the pathogen and in the development of new vaccines or treatments for the disease it causes. • Gene sequence data could, on the other hand, be used to reconstruct a pathogen (or one with its harmful characteristics) for deployment against a target population with no natural immunity
Synthesising pathogenic micro-organisms	• Synthesis of the genomes of viruses theoretically allows the introduction of mutations or novel sequences that can be used to study the function of particular genes or regulatory sequences. • Synthesis technology would obviate the need to source pathogens from natural reservoirs in other parts of the world or from other laboratories. It can facilitate reconstruction of extinct and could enable construction of novel pathogens.
Large-scale protein production employing heterologous expression systems (and associated production technology)	• Various heterologous systems (eg yeasts, bacteria, fungi) are engineered to produce recombinant proteins (eg antibiotics, laboratory enzymes) in bulk scale for legitimate commercial purposes. • Optimisation of large-scale commercial protein production systems (eg overcoming protein expression/folding/delivery issues) could also inform large-scale production of toxic proteins suitable for offensive purposes (eg botulinum toxin).
Optimisation of live attenuated vaccine production processes	• Optimal vaccines for several bacterial and viral pathogens involve strains that have had key virulence factors removed, either through serial passaging or by targeted genetic manipulation. • The production equipment required to produce a live attenuated anthrax vaccine (eg many veterinary anthrax vaccines) is identical to that needed to produce live virulent anthrax agent in bulk

6. In addition, Australia notes that certain other experiments that do not invoke the application of modern genetic techniques to the same degree as is likely for those in Table 1 are relevant to the BWC. These are listed in Table 2.

Table 2. Experiments relevant to the BWC that would not, necessarily, employ modern genetic technique

Experiment/technique	Relevance to BWC – the dual use dilemma
Enabling the weaponisation of a biological agent or toxin	• Understanding weaponisation processes may facilitate the development of protections against a potential BW incident. • Weaponisation for "threat assessment" purposes is likely to be interpreted by outsiders as simply the production of BW, thus endangering the norm against their production, driving a biological arms race, and making biological attacks more likely.
Any experiment with the smallpox virus	• Understanding variola is important for developing medical defences in the event that a smallpox outbreak occurred as a result of a BW attack or the accidental leak of the virus from a laboratory. • Because biosafety and biosecurity measures in laboratories are less than perfect, an increase in the number of personnel and facilities working with variola increases the likelihood of the virus escaping or being stolen and used in a biological attack.

Annex I

SYNTHESIS OF VIRUSES BY ASSEMBLY OF OLIGONUCLEOTIDES

(i) The polio virus, a virus with a genome size of 9kb (9000 nucleotides) was recreated artificially in 2002 after 3 years of effort (Cello *et al* 2002). The technology used the published sequence of the poliovirus genome, which is available on the internet, to produce short synthetic DNA oligonucleotides which were an exact copy of the poliovirus genome. These were then assembled by a complex process of ligation, sequencing and site-directed mutagenesis to form longer fragments (and some of these techniques involve gene technology). The longer fragments were then used to produce the wild type virus whose pathogenic characteristics were verified.

(ii) The technology used for this (synthesis of short ~60nt oligonucleotides) is applicable to any small virus whose sequence is already known. However, it is not suitable for the production of larger viruses such as the smallpox virus, which is 180,000 base pairs in length. This is due to the high error rate that occurs when lengths of DNA are produced (approximately 20% of sequences have errors when produced in this way).

(iii) New technology that can apparently generate long and accurate DNA sequences in a fraction of the time taken to generate the polio virus is currently under development. This technology involves the use of DNA synthesis on microchip arrays by a process called Polymerase Assembly Multiplexing. The question of whether developments in this field might necessitate some form of regulation has been the subject of recent debate among scientists, for example at the Second International Conference on Synthetic Biology held in May 2006 in the USA (http://pbd.lbl.gov/sbconf/).

(iv) Influenza virus, a 20kb RNA virus a variant of which was the causative agent of the Spanish Flu epidemic of 1918, has not yet been synthesised. This is because the sequence of the whole virus is unknown and cannot therefore be copied. However, it is estimated that within 3-5 years, the sequence of the virus will be published.

(v) Like the polio virus, it is possible that influenza virus could be synthesised by *in vitro* DNA synthesis. However, given the current limitations of DNA synthesis technology, it is more likely that a recombinant virus would be generated by a process known as reverse genetics in which segments from different influenza viruses can be combined together in a single cell to produce a genetic viral reassortment that can lead to a functional virus with characteristics of different viruses.

(vi) While technological limitation on *in vitro* DNA synthesis may preclude the synthesis of larger viruses such as the poxviruses of which smallpox is a member, there are other ways in which the smallpox virus could be recreated. Close relatives of smallpox such as camelpox virus and monkeypox virus are very similar in size to smallpox. The introduction of DNA changes into the genome of either monkeypox or camelpox might lead to a change in the host range of these viruses to include humans. However, until the complete DNA sequence of the smallpox virus is known, this approach is unlikely to succeed.