SCIENTIFIC AND TECHNOLOGICAL DEVELOPMENTS RELEVENT TOTHE BIOLOGICAL WEAPONS CONVENTION

Submitted by the Netherlands

1. This article discusses developments in science that have taken place since the Fourth Review Conference in 1996. It is necessarily limited to developments in the fields of biology, microbiology, biotechnology and molecular biology, including genomics, which relate or may relate to the BTWC. These developments are either 'new' (i.e. they did not exist in 1996), or are recent advances in terms of time, efficiency, costs, materials or necessary prior knowledge. In all cases they relate to 'dual use' techniques, in other words techniques that may be used for peaceful scientific or technological purposes in the pursuit of knowledge (and which are therefore legitimate), but which can also be misused to develop and produce biological weapons.

2. Generally speaking, two criteria have to be met in order to produce an effective biological weapon:

(i) a pathogenic (disease-causing) micro-organism or toxin has to be available in sufficiently large quantities to infect or poison a number of people;
(ii) an effective method of delivering pathogens or toxins which ensures that they penetrate the host while remaining active.

Both these criteria must be met for the biological weapon to work.

3. Over the last ten years new techniques for designing, producing and delivering pathogens/toxins have been developed and existing techniques improved. Using these techniques, it is in principle possible to make an advanced, second-generation biological weapon against which current methods of detection and therapy offer no protection. Some of the major new developments are briefly discussed below.

Recombinant DNA techniques

4. This is a collective name for all kinds of techniques designed to modify DNA or RNA in cells (plant or animal) and micro-organisms (bacteria, viruses, fungi). The result of such modification is usually that the organism acquires a specific property that is not natural to it, or it loses a specific property. These techniques are developing extremely rapidly while time needed, costs and complexity have been greatly reduced. At the same time, the number of techniques available, their efficiency and the range of possible uses have multiplied. This means that a much larger number of people have access to them. That said, laboratory expertise remains indispensable and the often heard suggestion that a secondary-school pupil could make a biological weapon of mass destruction remains a fable.

5. Examples of recombinant DNA techniques of relevance to BTWC include:

(i) **Fusion protein**: creating a single protein that combines properties from two different proteins. For example, through insertion of a toxin in a protein enabling it to identify

and kill specific cells. This principle is currently being researched with a view to killing cancer cells, but programming the toxin differently could make it possible to kill cells essential to life.

(ii) **Genome sequencing**: the speed with which the entire genetic complement of an organism including DNA and RNA (genome) can be sequenced is increasing rapidly, so that the number of organisms whose genetic code has been mapped is also rising fast. Analysis of the genome (genomics) of pathogenic micro-organisms and their virulence factors has created a substantial store of knowledge regarding disease mechanisms as well as a basis for new therapies, vaccines and medicinal drugs. But it is also possible to increase the pathogenicity of bacteria through genetic modification or to convert harmless bacteria into a pathogenic variant which as a result is difficult to detect, diagnose or treat. This can even happen by accident: in 2001 an Australian research group wanted to modify a mouse orthopoxpox virus with the aim of making mice infertile (in order to combat infestation). However, the modification unexpectedly produced a highly virulent virus that killed the mice even if they had been vaccinated against orthopox.

(iii) **Artificial synthesis of viruses**: in 2002 a group of American researchers synthesised a complete, fully functioning polio virus, based solely on the genetic code published on the Internet. Using this method it is *in principle* possible to make viruses that are difficult to obtain or even to resurrect one that has been eradicated (such as smallpox), as long as the genetic code is known. This latter possibility is particularly threatening since immunity (either natural or conferred through vaccination) has over the years disappeared in the human population. It should be noted that the structure of viruses is extremely simple in comparison to that of bacteria, let alone plants and animals/humans, and that the polio virus is probably the simplest of them all. All that is necessary to be able to build more complex viruses is time and study.

(iv) **RNAi (RNA interference or 'anti-sense' RNA)**: RNAi is a new method of putting a brake on cellular production of certain proteins. This distorts the way they function within natural bodily processes. RNAi is used in research to clarify the function of proteins and the mechanisms involved in physiological processes. In theory, it could be used therapeutically to halt undesirable processes or stimulate desirable ones. Misuse is equally conceivable.

(v) **Overproduction**: the production of proteins/fusion proteins by means of genetic modification of micro-organisms or plants has become much cheaper, efficient and less time-consuming. Now all kinds of proteins/toxins can be produced on a large scale, while in the past it was simply impossible to generate sufficient material to stage an attack.

Bioregulators

6. Bioregulators are substances that occur naturally in the body and regulate and coordinate countless physiological processes. They include hormones, signal molecules, enzymes and inflammatory mediators. Knowledge in this field has grown rapidly. It is now possible in a therapeutic context to intervene in order to boost desirable processes or slow down harmful ones. But misuse is equally possible. An excess of certain regulators (a relative concept since these

substances are active in extremely low concentrations) can lead to sleep disturbance and behavioural changes. Administering other regulators will lead to autoimmune reactions or, because they can affect blood pressure or cellular ion homeostasis, to heart rhythm disturbances, organ failure, paralysis, coma and death. Identifying the presence of bioregulators is extremely difficult since they are effective in very low concentrations and are naturally occurring substances.

Micro-encapsulation

7. One form of micro-encapsulation consists of enclosing micro-organisms or proteins in a coating or a biopolymer capsule. The aims of this process include preventing the substance being rendered prematurely inactive in the body or the environment, prolonging its shelf-life, ensuring that a substance/medicine is released over a longer period of time and ensuring that the substance passes through the stomach intact if it is intended to be absorbed in the bowel. Considerable knowledge on how to achieve these aims efficiently has been made widely available. However, the same techniques make it possible to spread peptides, proteins (toxins, bioregulators) and micro-organisms while avoiding the problem of rapid inactivation.

Penetration enhancers

8. These agents enhance the ability of substances or micro-organisms to penetrate the skin or mucous membranes and were originally developed to improve the absorption of medicinal drugs. They also lower the threshold at which micro-organisms or toxins become harmful, making new routes for the delivery of biological weapons possible.

Nanotechnology

9. This technique combines biotechnology, synthetic biology (producing molecules with a specific function by artificial means) and information technology to design molecular structures capable of performing a wide range of functions. Existing biological processes are often imitated but the structures are tailor-made to the desired size. Nanotechnology is still in its infancy (just five years old) but spectacular results have already been achieved. In 2004, for example, a molecule was designed that operates completely independently (identifying and cutting RNA), and a contact lens that releases accurate amounts of a drug to combat eye disease. This is an enormous growth industry that in commercial terms is expected to l eventually put the pharmaceutical market in the shade. Possible applications include a number in the medical sector, such as targeted delivery of therapeutics by nanoparticles, microsensors or implants made of biological material that are smaller and more effective than current implants. The synthesis of a biological weapon, or a military application for nanotechnology, is only a question of time if the necessary research is carried out.

Proliferation of knowledge

10. The biotechnology industry has become more complex and more global. While it was once concentrated in Western countries, nowadays Brazil, China, Cuba, India, Singapore and South Korea are all host to high-quality biotechnology firms. The number of large, market-dominating companies has declined through mergers and take-overs, but their size has grown

considerably. At the same time there is a movement towards specialisation in the form of measures to strengthen core activities at the expense of subsidiary activity. The desire to cut costs and secure a strong position in particular market segments has driven these changes. Alongside this, there are many small businesses that occupy niche markets and specialise in developing, manufacturing and selling a very limited number of products or techniques. Failure of a product often means bankruptcy, while success often leads to acquisition by a larger firm. The number of business start-ups and the failure rate are very high in this sector, and only relatively few companies gain a foothold in the market. Although a great deal of innovative research is still being done by the large companies, part of it has been outsourced to manage risks and cut costs. Innovative research is also being done by universities, government laboratories and small firms established as spin-offs of university research. This means that in the context of non-proliferation and BTWC compliance, it is not only the traditional, large pharmaceutical companies, universities and government laboratories that need to be monitored, but also smaller firms. Records of companies active in the sector need to be regularly updated.

Threat

11. There are three stages in making a biological weapon:

(i) Obtaining a pathogenic microorganism or toxin; possibly increasing its pathogenicity or tinkering in some other way with its properties (second-generation biological weapon);
(ii) Production;
(iii) Incorporating it into a suitable delivery mechanism.

12. After every stage checks should ideally be carried out to test whether the organism still does what it is intended to do. Assembling the necessary knowledge and equipment, funding, production and testing all leave clear traces (the footprint). In general, it can be argued that the bigger the objective (making people ill, killing them), the more technically difficult it is to achieve; in other words, the greater the number of resources, people, tests etc. are needed and therefore the bigger the footprint left behind. Experience with the Aum Shinrikyo sect (who made eight attempts in Japan between 1990 and 1994 to make a crude biological weapon for attacks in Tokyo and its vicinity using anthrax or botulinum toxin) shows that it is not as easy as is sometimes suggested to make an effective biological weapon. Nor is it easy for an individual or group of people to go about such a task without eventually alerting the authorities. Although developing a second-generation biological weapon is in principle possible, the footprint left behind is much bigger than the one created by a ‘first-generation’ weapon. The former requires more knowledge, qualified personnel, materials, costs, tests and much more time. It would therefore seem logical to assume that the chances of an individual or group within a stable society developing a successful biological weapon are extremely small, and that the chances of their developing a second-generation weapon are much smaller. Nor are applications involving nanotechnology as yet within the reach of groups or individuals.

13. Of course, the situation would radically change if a group operating within a destabilised society was to be supported passively or actively by the government, particularly if that government was itself leading the programme. Successful production would then be merely a question of time. Up to 1995, the biological weapons programme in the former Soviet Union

showed all the characteristics of research into and production of second-generation biological weapons (genetically manipulated agents with multiple resistance to antibiotics, designed to sidestep vaccination or produce bioregulators, or consisting of fusions of two different viruses (chimeras). (Alibek & Handelman)

Consequences for the BTWC and the Sixth Review Conference (2006)

14. The current wording of Article I and the related Additional Understandings as adopted at the Second, Third and Fourth Review Conferences is in principle so general that it prohibits virtually all second-generation biological weapons and all recent developments except where intended for peaceful purposes. The key sentence reads as follows: "…the Convention unequivocally covers all microbial or other biological agents or toxins, naturally or artificially created or altered, as well as their components, whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes." This formulation covers not only misuse of all naturally occurring biological material, but also all derived forms. In other words, all developments in the fields of genetic modification and artificial synthesis of viruses, and all related work which makes use of micro-organisms and their component parts are already covered by Article I. An important exception is nanotechnology. Analogous to the example referred to above of the artificial molecule that can cut RNA, one could imagine that in the future microscopic machines built of DNA and protein particles could be made to intervene in biological processes by imitating the effect of an enzyme or toxin. This degree of artificiality might exclude the technology from the Convention. To prevent misunderstanding, we recommend including in the Additional Understandings a provision to the effect that misuse of scientific and technological developments in the field of nanotechnology and derived applications is in fact a violation of Article I.

15. Prohibiting or otherwise hindering legitimate research using modern molecular and microbiological techniques whose results would benefit humanity in general is not the way to prevent the production of biological weapons. The answer lies in improving investigative techniques to identify footprints, encouraging openness among researchers and announcing and complying with confidence-building measures in order to discover state-sponsored programmes.

References

1. Alibek, K. & S. Handelman, *Biohazard*, 1999, Hutchinson, London, UK.
2. Development, Security and Cooperation and Board on Global Health, *Globalisation, Biosecurity and the Future of Life Sciences*. Chapter 3: Advances in Technologies with Relevance to Biology: The Future Landscape. Source: http://darwin.nap.edu/openbook/0309100321/gifmid/139.gif. Accessed 21-7-2006.
3. Development, Security and Cooperation and Board on Global Health, *An International Perspective on Advancing Technologies and Strategies for Managing Dual-Use Risks: Report of a Workshop (2005).* Chapter 4: Emerging and Converging Technologies. Source: http://darwin.nap.edu/openbook/0309096820/gifmid/57.gif. Accessed 21-7-2006.