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**BACKGROUND PAPER ON NEW SCIENTIFIC AND TECHNOLOGICAL
DEVELOPMENTS RELEVANT TO THE CONVENTION ON THE
PROHIBITION OF THE DEVELOPMENT, PRODUCTION AND
STOCKPILING OF BACTERIOLOGICAL (BIOLOGICAL) AND
TOXIN WEAPONS AND ON THEIR DESTRUCTION**

Prepared by the Secretariat

1. In paragraph 22 of its report (BWC/CONF.V/PC/1), the Preparatory Committee for the Fifth Review Conference 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 decided to invite States Parties that wished to do so, including the Depositary Governments, to submit to the Secretariat information on new scientific and technological developments relevant to the Convention. This information should cover the applications being made of such developments and their relevance to various aspects of the Convention.
2. The present document contains the information provided by States Parties to the Secretariat, as of 14 September 2001, pursuant to paragraph 22 of the report of the Preparatory Committee.

Bulgaria

The National Centre for Infectious and Parasitic Diseases with the Ministry of Public Health, being the country's only scientific-practical institution, produces more than 700 types of biopreparations of bacterial, viral and parasitic origin designed for specific diagnostics, treatment and prevention of infectious and parasitic human diseases, on the basis of classical and modern bacteriological methods. The National Centre promotes intensive scientific-research aimed at improving the quality of produced bio products, as well as for their in-depth study in experimental or epidemiological test conditions. Its scientific research work is not related to the development or study of any form whatsoever of bacteriological (biological) weapons. The purpose of this research work is to develop the scientific approaches to combating infectious and parasitic diseases, as well as to exercise constant control on the spreading and character of infections and parasitic diseases in the country.

The Bulgarian Academy of Sciences conducts research on the development of anti-viral chemotherapeutic agents, efficiently capable of treating and directly preventing particularly dangerous viral infections caused by the Flavy- and Toga-viruses family. The programme for screening of anti-viral substances envisages the inclusion of Poxviruses, with the purpose of finding effective chemotherapeutic means against variola.

Research on the *Yersinia* genus (*Yersinia enterocolitica* and *Yersinia pseudotuberculosis*) pathogenic representatives is also conducted with the aim of developing mucous vaccines against the classical disease of swine pest, which causes enormous economic losses. Fundamental research is carried on as well in view of revealing the factors and mechanisms of bacterial virulence with certain pathogenic agents of epidemiological and epizootic significance - *Listeria monocytogenes*, *Salmonella typhimurium*, and *Francisella tularensis*. No genetic research is conducted with the above-indicated agents for the purposes of modeling their virulence.

South Africa

Introduction

1. Although there have been many scientific and technical developments relevant to the Convention since the fourth Review Conference, this paper will concentrate exclusively on developments in terms of biocontrol agents and plant inoculants.

Biocontrol agents and plant inoculants

2. In all work related to the BWC, the threat against plants is usually considered to be of lower importance than the threat against humans. Therefore, a lower priority is given to plants in any work done in the context of the Convention. Issues related to plants are either not addressed, or it is reasoned that plants are of lesser importance and more difficult to protect.

3. This situation occurs despite the fact that major elements of all past BW programmes since the 1920's were directed against crops; and numerous plant pathogens were researched, developed and produced as weapons. A variety of delivery systems, specifically for anti-crop warfare, were also researched and developed. In addition the majority of recent allegations - whether substantiated or not - refer to plant and crop diseases.

4. Plant inoculants and biocontrol agents are two elements that play a role in the threat against plants in the sense that they have the potential of being easily diverted into BW. As in the case with vaccines, they are also produced in facilities that by their nature have the capability of producing BW.

Plant inoculants

5. The use of bacterial, fungal or viral inoculants in crop, fruit and forestry production is a universally accepted practice and is increasingly being expanded to domestic use such as gardening. The industry producing these substances is growing rapidly and becoming more sophisticated.

Definition

6. A plant inoculant is a formulation containing pure or predetermined mixtures of living micro-organisms for the treatment of seed, seedlings or other plant propagation material for the purpose of enhancing the growth capabilities or disease resistance of the eventual plants or crops.

History

7. Research to improve plant growth dates back more than 100 years. Researchers concentrated on the supply and availability of nitrogen and phosphate because they are the most essential nutrients necessary for plant growth.
8. In 1898 the first inoculant consisting of soil bacteria, which provided nitrogen to legume plants when introduced to the plant, was commercialised. These bacteria are still utilised today and much research is being conducted on them.
9. Work continued to find phosphate solubilising micro-organisms, but the first was only discovered in 1982 in Canada where a *Penicillium* fungus species that could make less available forms of residual soil phosphate available for plant use was discovered. An inoculant containing this fungus was commercialised in 1991.
10. By 1996 the first combination phosphate, nitrogen inoculant was available.
11. At present various natural or recombinant micro-organisms providing a range of nutrients as well as protection to plants are used in inoculants. Various substrates and delivery methods have been developed and are developing at an increasing tempo.

Purpose

12. Plant inoculants are used:
 - a. To stimulate roots, to improve growth.
 - b. To germinate seeds.
 - c. To provide growth factors and nutrients.
 - d. For disease prevention and control.
 - e. To enhance or restore ground micro-flora.

Mode of Action

13. Plant inoculants act in one or more of the following ways:
 - a. Direct action. The micro-organisms infect the root hairs of the plant and cause the root cells to swell, and form nodules. Within these nodules, the bacteria convert nitrogen from the air into a form the plant can use as a nutrient. They are classified as nitrogen inoculants and work mainly on legume plants.
 - b. Indirect action. These inoculants work by turning mineral forms of less available soil phosphate and other nutrients into forms immediately available for the plant to use. These are usually mixtures of strains of indeterminate origin and supplied as starter kits to farmers for on-farm fermentation in order to produce large volume cultures.

- c. Protection. They provide protection against specific pathogens such as *Agrobacterium radiobacter* strain K84 against crown gall or certain fluorescent *Pseudomonas* strains against non-specific rootrot complex pathogens; their action is similar to biocontrol agents.

Types of inoculants

14. The best known nitrogen inoculants are the bacteria *Rhizobium* or *Bradyrhizobium* used in the production of legumes. These inoculants consist of large numbers of viable cells of carefully selected strains or mixtures of strains of the *Bradyrhizobium* or *Rhizobium* species for the treatment of specific legume species or varieties. Successful inoculation results in a symbiosis where atmospheric nitrogen can be utilized, thus making the legume independent of soil or fertilizer nitrogen.

15. Vascular Arbuscular Mycorrhizia (VAM), which is a fungus and is effective on a wide variety of plants, is most commonly used today to enhance the uptake of phosphates, potash and other nutrients. They are also used to improve plant resistance against diseases, environmental stresses and destructive arthropods (note that as in the case of rhizobia, VAMs infect the roots of the target host plant). Most VAMs cannot be produced on artificial substrates. Another type is *Penicillium bilaii* which solubilises phosphates although the organism does not infect the host plant.

Methods of inoculation

16. Inoculants can be applied as a seed dressing using powder-on seed or direct in-furrow application using granular products or liquid formulations. Liquid formulations can now be applied through irrigation systems or specially modified sprayers (as used for compost teas especially for plant disease control). The method of application is dependent on the type of bacterial carrier or preservation method used.

Production

17. The traditional and still most common legume (*Rhizobium/Bradyrhizobium*) inoculant used outside the USA in developing countries is the sterile peat based inoculant. The product consists of finely ground (200 – 400 mesh) stabilized sterile peat with approximately 10^9 viable cells/gram carrier and is sold in 250g units. This is the inoculant of choice in environments lacking sophisticated technology because they can be produced in large quantities by means of a peat based process and in reasonable quantities by unsophisticated means, such as using modified soft-drink bulk canisters as fermenters.

18. Carriers such as sintered granules, clay minerals or liquid are used in more technically sophisticated environments. Concentrated living cell preparations are produced and can be purchased as pastes or frozen suspensions. The production of inoculants through these methods necessitates the use of industrial sized fermenters, large capacity in line flow centrifuges and sterile filling stations.

Relevance of plant inoculants for the BWC

19. As the industry grows more sophisticated production facilities are established and the greatest relevance for the BWC is the fact that these facilities have the potential to be converted to BW producing facilities, as in the case of vaccine production facilities. Furthermore, much genetic research and development is conducted to improve the micro-organisms that form the active ingredients of inoculants.

20. The development of liquid inoculants may in future add to the relevancy of these agents in the sense that application by spraying and aerosolisation is a possibility.

Biocontrol agents

Biological Control

21. Biological control is based on the utilisation of a specifically chosen living organism to control another. Insects, mites, bacteria and fungi are thus used to control insect, mite disease and weed pests in order to protect food or fibre crops as well as for controlling alien vegetation in sensitive environments.

22. Utilisation of biological control and destruction of plant disease, pests and weeds has developed rapidly over the past 10 years. Much attention has been paid to improvement of the process of biological control, increased effectiveness of agents, increased production of agents, including recombinant organisms, and more effective means of application. Investigation of indigenous natural enemies of pests and their impact on such pests is also intensifying.

23. Recently biological control was extended to the application of biocontrol agents against plants, and work is in progress to apply it to certain crops as well.

Biological agents

24. A Biocontrol agent can be defined as a living organism or biologically active substance originating from such an organism, used for the prevention, elimination or reduction of plant diseases, pests or unwanted plants.

25. The ideal biocontrol agent should be completely specific for a particular pest, must have a high effectivity against its target, and have a low level of susceptibility to other environmental factors.

Approaches to biological control

26. There are three main approaches to biological control:

- a. Classical approach. This approach involves identifying and finding specific biocontrol agent(s) against a specific pest(s) and introducing them into the area where the pest is present. This approach may include travelling to other areas or other countries from where pests originate.

- b. Augmentation. Augmentation is a method of increasing the population of a biocontrol agent by mass production in the laboratory and then releasing them into an area. It also includes the breeding of biocontrol agents, which can attack or find their prey more effectively. Mass release of biocontrol agents, when the pests are most susceptible or in such large quantities that most pests are affected, is a part of this approach.
- c. Conservation of natural enemies: This implies the identification of any factors that may interfere with the biocontrol agent and reduce its numbers as well as the provision of required resources to support the biocontrol agent.

Factors affecting application

27. Prevention Vs Treatment: Biocontrol agents have the greatest effect when released as a preventative measure. They should thus be introduced before the pest infestation has reached a point where they are unable to prevent the pest population level from developing to damaging levels. This rule will obviously not apply to the more recent use of biocontrol agents against plants and crops, although in this case they will be more effective against young plants than against full-grown plants.

28. The population level of pests at the time of release: If the pest population level is too high the biocontrol agents may not be able to act quickly enough to protect the crop. If the pest population is very small it may not be necessary to release any biocontrol agents, provided such agents are already present in the area.

29. Seasonal factors: Some biocontrol agents are more active at certain times of the year than others.

30. Time of the day: The time of the day may be important especially if the release is to be made in the open air.

31. Temperature: Temperature can have a dual effect on the effectiveness of biocontrol agents. Some biocontrol agents, such as insects, are more active during the warmer part of the day. They may, however, disperse from the area more easily if they are too active. Other biocontrol agents such as some fungi, prefer lower temperatures while, higher temperatures can cause increased mortality of some biocontrol agents.

32. Weather: Weather conditions such as rain, wind and humidity may have a negative effect on agent survival during release.

33. As a general rule, biocontrol agents should be released during the cooler part of the day (early morning or late afternoon), under favourable weather conditions and at a time of year that is most favourable to the agent.

Biocontrol agents against plants

34. There is increased use of biocontrol agents against plants to control either noxious or unwanted plants or crops. Such activities include:

- a. The implementation by States of active programmes to destroy alien plants that have become pests due to a lack of natural enemies in those specific States through the use of biocontrol agents. These same plants are, however, not pests in their countries of origin and are in some instances utilised commercially in those States.
 - b. The programmes to develop *Fusarium* fungi to attack cannabis and coca plants, and *Pleospora* fungi against poppy plants for drug control purposes.
35. These activities require closer scrutiny and control as the distinction between the peaceful use of biocontrol agents under these circumstances and their use as BW is less clear and the dual use nature of these agents is much more relevant, for the following reasons:
- a. Natural enemies of plants and crops are used, which may not be specific enough to ensure that they do not attack other plants in the area.
 - b. Undesired plants, exotic plants or even noxious plants in one country may be natural, essential and in many cases utilised for commercial purposes (crops) in other States.
 - c. Biocontrol agents are more difficult to use than pesticides and if they are not used correctly in terms of time of use, dosage, etc, they may not be successful, but they may have an effect when not required.
36. Considerable effort goes into research to find natural enemies that are totally specific, to improve the effectiveness of these agents, and to increase the success rate of their application. This research and development could easily be diverted for non-peaceful purposes.

Conclusion

37. Plant inoculants are relevant in terms of:
- a. A growing industry and more sophisticated production facilities that have the potential to be diverted to BW producing facilities, as in the case of vaccine production facilities.
 - b. The genetic research and development that is conducted to improve the micro-organisms that form the active ingredients of inoculants.
 - c. The development of liquid inoculants that will make their application by spraying and aerosolisation a possibility.
38. Biological Control of plant pests, weeds and plants is relevant to the BWC in terms of:
- a. The less clear distinction between the peaceful use of biocontrol agents and their use as BW due to the dual use nature of these agents.
 - b. Undesired plants, exotic plants or even noxious plants in one country may be natural, essential and in many cases utilised for commercial purposes (crops) in other countries.

- c. The research and development that could easily be diverted for non-peaceful purposes.
- d. A growing industry and more sophisticated production facilities that have the potential to be diverted to BW producing facilities, as in the case of vaccine production facilities.

39. It is clear that plant inoculants and biological control of plant pests, weeds and plants are relevant to the BWC and, therefore, they references to them should be included in the final declaration on Article I. Under Article V, the CBM declarations should also be expanded to provide for declaration of plant inoculant and biocontrol agent production facilities.

Sweden

Introduction

The development within the field of biotechnology continues to be fast and innovative, especially in the field of medicine. Part of this development is of concern to the BWC and can also contribute to improvement of the picture of compliance.

Our increased understanding of the molecular mechanisms behind microbial infections and of other diseases together with the information revealed by the complete sequence of the human genome has dramatically changed our way to develop both pharmaceuticals and vaccines. Bioinformation in combination with chip technology has opened the possibility to detect differences in gene expression and early signs of disease. The chip technology has also increased our ability to identify microorganisms, even at the level of strains. Combinatorial chemistry and automated tools for high throughput screening have improved the prospects of finding new drugs. Our increased understanding of how the immune system defeats disease is also of utmost importance in the development of new drugs. Some of the techniques that fueled the development of biotechnology during the last five years have brought us several new pharmaceuticals produced by recombinant-DNA methods.

Genomics, proteomics and treatment of disease

The sequencing of the human genome is completed and this has markedly affected the approach to find new targets for treatment of diseases. The structural diversity within the proteins encoded by the genes in the human genome is considerably greater than the small number (30,000 - 40,000) genes might suggest. This increased level of protein functionality has been achieved by iterative evolution and alternative splicing and generated a combinatorial diversity at the protein level, resulting in the human proteome, with high complexity. If a disease-inducing element is introduced to cells, it may change how much gene product is made, when the genes are turned on, and how these events affect other genes. These effects will determine if the organism successfully defends itself or succumbs to the disease. The study of this dynamic, proteomics, has the potential to reveal new targets for drug intervention in disease processes and focuses on the protein products of the genome and their interactions rather than on simple DNA sequences. Many different strategies, e.g. screening libraries of organic molecules and peptides, structure based drug design as well as identifying genes for inherited diseases, are explored to identify new pharmaceuticals.

Structure-function relationships are at the forefront of this research and the field of functional genomics will narrow the choice of therapeutic targets to a practical range. Projects focused on the structural genomics of various pathogenic organisms will provide unprecedented opportunities for structure-based drug design and simultaneously provide expression systems for proteins to be used in high-throughput screening and combinatorial chemistry approaches. Differences in gene expression levels in cells that are diseased versus those that are healthy can be detected by DNA-based chips technology. The understanding of these differences in gene expression not only serves as a diagnostic tool, but also provides drug makers with unique targets that are present only in diseased cells. In addition to DNA and RNA-based chips, protein chips are being developed, which can be used to study interactions between proteins at very low densities.

Gene therapy in the context of gene delivery to cancer cells as well as to cells lacking a gene function continues to be explored. In either case, considerable challenges remain: e.g. delivery problems, instability of expression and unpredictable immune responses still remains. However, new viral and DNA vectors as well as methods for transfer to different types of cells are improving. Insulin genes, as an example, delivered by DNA-plasmids, are taken up by and expressed in epithelial cells of the intestine, and can thus compensate the loss of normal production of insulin.

Another rationale that is considered important in cost-effective drug design is pharmacogenetics and pharmacogenomics, or “individualized medicine”. Gene sequence data alone is of little clinical use unless it is directly linked to disease relevance. DNA-based chips are used for detection of mutations in specific genes as diagnostic markers of the onset of disease. Human populations with different geographic origins, have different frequencies of many alleles studied. The consequence of polymorphism on drug action will become more relevant to meet, as small-molecule and peptide drugs are increasingly targeted at specific proteins encoded by disease genes and receptors. A consequence of this ethnic variation will probably be a broad variation in the drug response. Pharmacogenetic studies may in this way improve the safety and the efficiency profile of drugs but can also lead to market segmentation. This development should be kept in mind and closely followed as it relates to Articles I and X of the Convention.

Macromolecular combinations (e.g. DNA shuffling, RNA and DNA aptamers or mRNA-protein fusions) when combined with high throughput screening methods will allow proteins and nucleic acids with a vast array of novel properties to be produced. This vast development of new therapeutic agents with activities covering the entire living system will lead to fine tuned control of human diseases. Even a small imbalance in these substances could have serious consequences.

Our understanding of the molecular mechanisms of microbial infections has increased immensely over the last decade. A number of methods have been developed which allow studies of the development of infectious diseases at the molecular level. Many of the key molecules (virulence factors) that pathogens use to cause disease have in this way been identified. The study of the interaction between human cells and microorganisms during infection is one driving force and of fundamental importance for the development of new means to defeat infectious diseases.

As antibiotic resistance increases into a major public health problem, the race will intensify between microbes and novel drug discovery and development efforts. Constant efforts to innovate around issues of resistance and genomic decoding of many of these organisms will help accelerate the validation of multiple targets against which new antimicrobial agents are to be developed. Antimicrobial peptides are one starting point of multiple efforts to develop new agents that are effective against a variety of microbes, including viruses. There are many examples of different very promising approaches, including peptides derived from synthetic combinatorial libraries, defensins and several peptide bacteriocins.

New systems monitoring expression of genes during various infections have been developed. It is, for instance, possible to identify genes that are activated by or essential for a pathogen in certain organs, in the immune system or inside human cells. These new methods will be instrumental in the development of new means to control infectious diseases. In this way, as an example, a molecule that allow cellular entry of the Ebola and Marburg viruses has been identified. This insight might point the way to novel treatment of and vaccine strategies for these two infections.

Among all the substances tested, in this broad field of research, there will be many that will be classified as harmful or toxic to all types of life processes and not suitable in medical treatment. These molecules can affect e.g. mental processes, consciousness, body temperature, and emotion and be toxins. These substances would be very difficult to detect if used in a hostile manner. As a consequence it is important follow to the research in this field and to evaluate the results as they are of concern to the BW Convention. Whole organisms, both higher organisms and microorganisms, can be subject to similar rapid evolution and be of interest to those with malevolent aims. This worldwide increase in knowledge in life sciences may be misused and increase the risk of hostile use of biological active agents, whether natural or developed. The problem with antibiotic resistance will remain and can obviously be used to manipulate microorganisms to increase their attraction as BW agents.

Vaccines

Vaccine development starts with the identification and production of antigens, a process that DNA sequencing greatly has accelerated. The complete sequence of many pathogens has been determined and the sequence acquisition will continue to increase. The techniques of molecular biology can help distinguish which antigens are useful and thus could be included in a vaccine.

Recombinant vaccines, that express foreign genes, have been attracting a considerable interest during the last decade. Among these are recombinant vaccines that produce immunity against specific pathogens; others are proteins functioning either by binding to cell surface molecules to regulate cell functions or by catalytically modifying specific substances e.g. toxins and other toxic compounds. Many new concepts to develop such vaccines have been explored but only a minor part have been successful, e.g. the creation of multivalent vaccines.

Techniques of molecular biology can also pull out a given subset of additional genes that are needed in the context of e.g. DNA-vaccines. Sequencing will also be used to evaluate genetic variation between isolates of the same pathogen and techniques like DNA-shuffling utilized to create hybrid-genes capable of eliciting protection through vaccination against all

disease causing variants of a pathogen. DNA-based vaccines have the capability of inducing both humoral and cell-mediated immunity and can be used for efficient large-scale production, but have not so far proved very effective in humans. This may be because the way of administration just induces a weak immune response.

Vaccine research is not solely focused on antigens. The effectiveness of the immune response in protecting patients against subsequent disease depends both on the nature of the specific antigens and on the general stimulation of the immune system. The increased understanding of the function of the immune system has shown the importance of the nature of the immune response triggered by the vaccine to induce protection.

This knowledge was the driving force for a research team in Australia to limit the problems caused by mice on corn during storage. A gene affecting the immune system was used to modify a mouse virus, related to smallpox. The aim was to develop a vaccine to function as a contraceptive. The result was unexpected and the induced cascade of immune reactions led to high death rate within the population of mice. The research team could also reveal that traditional vaccination against mousepox gave an incomplete protection against the modified virus. This example shows how unexpected results of research for peaceful purposes can play in the hands of those with malevolent aims. It also indicates how important it is with transparency and possibility to follow the development in the area of life sciences to be able to address compliance concern.

Industrial microbiology and production

The greatest impact of biotechnology during the last five has been in treatment of rare diseases. Notably features of the resulting biopharmaceuticals are their innovative mode of action and the minute amounts need in therapy. That is the total amounts needed to treat orphan diseases will be in the range of kilos rather than tons, compared to antibiotics used to treat infectious diseases. As a consequence of this development the majority of the system used for production of new pharmaceuticals is or will be perfusion bioreactors and the amounts produced will be small. The consequences of polymorphism on the development of new therapeutics will also affect the way of production and the amounts produced. All this will add to the picture of compliance concern and make it more complex.

Large-scale production of biological active substances, with a microbiological origin, in relatively small production facilities, is also possible due to biotechnological development. Within the pharmaceutical industry research is intense for methods to stabilize drugs for aerosol or oral delivery of, for example toxins, chimeric toxins, modulators of the immune system and bioregulators. The outcome of this research could also increase the risk for development of more stable biological and toxin weapons.

With the fermentation techniques available today, a military significant supply of BTW agents, with increased stability, could be produced over a short period of time, obviating the need for the long term stockpiling of agents. As a consequence, a BTW production facility could be used for other purposes during peacetime.

Identification of disease causing agents

The classic and time-consuming procedures methods for identification of infectious agents, cultivation followed by biochemical analysis are being complemented by rapid immunological and genetical methods. An immunological method identifies the agents through antibodies and fielded systems are available. However, the method has limited sensitivity and usually needs an amount larger than the infection-dose for a positive identification. The development of protein-based chips will improve the sensitivity and the specificity of this type of analysis. In parallel with the development of protein-based chips aptamers are tested as a replacement for antibodies. Aptamers are more stable and cheaper and more easy to produce.

The development of genetical based methods for identification, in which the DNA gives a fingerprint, is very fast. These methods are usually more reliable and sensitive than the immunological ones. DNA-based chip is one technology that can be used to reveal phylogenetic relationships and identify organisms at the level of strains. As already mentioned, DNA-based chips can also be used as a tool in diagnosis.

This development in microbial identification and diagnosis of disease has improved prophylaxis and therapy and is also be beneficial for the BW Convention in making it possible to distinguish between endemic strains of microorganisms and BW agents introduced from the outside.

Most NATO countries are establishing NBC-response teams, with responsibilities, among others, for sampling and identification of B-agents in events of hostile use. These teams are equipped for, sampling and identification of B-agents in all types of environmental samples. The awareness of the threat of biological weapons and the preparedness for this is beneficial for the BW Convention, as it will increase the risk of disclosure.

Conclusion

Since the last Review Conference in 1996 the research in the field of biotechnology and molecular biology have entered a new and more complex era. Huge amount of knowledge concerning basic principles of life have found worldwide applications in solving problems of global interest, such as public health, animal health, agriculture and protection of the environment. The research is focused on molecular targets and is organized around the mechanisms underlying disease processes. While these developments have been and are mostly beneficial they can also be misused. Biotechnology could be used to create an increasingly complex set of pathogens and toxic molecules targeted at humans, plants or animals, a matter of greatest concern to the Convention.

The new knowledge will also give countries the possibility to develop defensive tools and methods for early detection and precise identification of disease causing organisms and toxins, and thereby increasing the possibility to detect hostile use. The awareness of the threat of biological weapons will be beneficial to the Convention, as the preparedness for it will increase the risk of disclosure. The potential for improving defensive measures against possible BW attack as well as the increased possibilities of disclosure will obstruct proliferation.

Sweden is of the understanding that Article I of the Convention is sufficiently comprehensive and covers the current developments in areas relevant to it.

United States of America

1.0 Introduction

1.1 In preparation for the 2001 Review Conference on the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and their Destruction (BWC), the Preparatory Committee requested preparation of national papers on new scientific and technological developments relevant to the Convention.

1.2 Since the 4th Review Conference in 1996, there have been significant advances in the field of biotechnology. The major advances have occurred in the fields of genetic modification, genomics, proteomics, bioremediation, biocontrol agents, vaccine development and bioinformatics. Of special interest to the BWC are applications in directed molecular evolution (i.e., genetic modification), proteomics, bioinformatics, and vaccinology. The number of countries which are developing and enhancing their biotechnology capabilities continues to grow as the applications continue to expand into commercial sectors and the resulting industry has expanded in both scope and products developed and marketed. All of these trends continue to have practical significance for the BWC.

1.3 The pace of advances in biotechnology will increase. To stay abreast of this trend, we must maintain a broad overview of numerous fields ranging from basic research and development through manufacturing in such areas as: biotechnology, molecular biology, life sciences, medicine, microbiology, bioinformatics, computational biology, and pharmaceutical and vaccine production. Our focus should include the academic community, government agencies and departments, as well as industry. Advances in genomics, proteomics, computational biology, and industrial biotechnology remain a BWC concern. While offering obvious benefits to mankind, advances in technology can be used to produce new substances or modify old ones and lead to novel and significant toxins and biological or biochemical weapons threats. Nations should remain cognizant of and carefully monitor for potential abuse of these evolving technologies.

2.0 Advances in industrial application of biotechnology

There are a number of areas where advances in production as well as new product technology have relevance to the Convention. These will be detailed in the following sections:

2.1 Advances in Production

2.1.1 Biocontrol agents: Biocontrol is defined as the use of live organisms such as bacteria, viruses, or the products of microbes such as natural products and toxins, to control agricultural pests. An expected surge in demand for biopesticides arising from increasing environmental awareness has failed to materialize. The lack of demand for biopesticides has resulted from the fact that biopesticides, are: (1) not as effective or consistent, (2) work slower, (3) cost more to produce, (4) have a limited pest spectrum, and (5) are more difficult to store when compared to chemical pesticides. Given such limitations, all of these factors affect the viability of this technical discipline. For the immediate future (i.e., the next 5 years) the commercial potential

of biopesticides will focus on “niche” markets where use of chemical pesticides is limited. In general, pathogens and microbes are very specific for one pest or target species. This can be a problem in biocontrol of weeds, where fields might contain 10 to 15 species of weeds, making single weed bioherbicides cost prohibitive. Insect pests are usually limited to one or two species so the use of a specific pathogen is not as big a hurdle with bioinsecticides. Consequently, more organisms are in use as bioinsecticides

2.1.2 Natural products of both fungal and bacterial origin have been developed as potential biopesticide products. Natural products can be used directly as biopesticides or they can serve as templates for the development of new areas of chemistry for conventional pesticides. The most significant group of biopesticides is based on an endotoxin protein derived from strains of a soil borne bacterium, *Bacillus thuringiensis* (Bt). For years Bt was only available as a sprayable microbial product but with the development of recombinant DNA technology, the gene for the Bt toxin has been inserted in several crops. This has resulted in crops (e.g. corn, cotton, potatoes) that are resistant to several important insect pests. Currently, biopesticides capture a mere 1.4% or \$380 million of the \$28 billion dollar global market for pesticides. If the fundamental mission of biopesticides is construed to be the continued reduction of chemical pesticide use then they are clearly not achieving their desired goal.

2.1.3 From a technology viewpoint, the biocontrol industry relies on adapting technologies, rather than internal R&D, developed either within the biotechnology industry itself or the discovery of the “efficacy of an extract” from a plant or microbe during high throughput screening of naturally produced compounds. Reliance on adaptive technology makes it highly unlikely that biocontrol would be a source of unique or special processes or techniques that would enable BW proliferation. This is not to say that facilities used to produce biocontrol agents couldn’t be exploited for dual-use purposes. For example, facilities that produce Bt (*Bacillus thuringiensis*) as a biopesticide could easily be converted to produce anthrax (*Bacillus anthracis*) within a matter of days. However, this is not unique to this industry.

2.1.2.0 Bioremediation: Bioremediation is the use of microorganisms and other biological systems to remove environmental pollutants. In most instances it involves the use of naturally occurring biological processes to cleanse the environment of pollutants that may be toxic or otherwise harmful to human health or ecological processes. As such bioremediation has been viewed as a green solution to pollution brought on by human activities. This topic has been the subject of a number of review articles and books and was the focus of a task force of the Organization of Economic Development and Cooperation, which issued a report on biotechnology for a clean environment. There are three approaches that are currently used for bioremediation.

2.1.2.1 Natural attenuation: The first approach, termed natural attenuation, involves a total reliance on naturally occurring biodegradation to remove an environmental pollutant. This clearly is a green process as there is no intervention to alter the natural fate of a pollutant. The problem is that the process is often very slow and often incomplete. Thus, it does not remove toxic substances fast enough to preclude adverse ecological consequences due to pollutants. Nevertheless, natural attenuation has become the method of choice in Europe for treating marine oil spills.

2.1.2.2 Environmental modification: The second approach is to accelerate a natural process through environmental modification. For example, in the case of oil spill nitrogen and phosphorus fertilizer can be added to overcome rate-limiting nutritional factors. This increases the rates of oil biodegradation by allowing for greater growth of hydrocarbon-degrading microorganisms, just as adding an agricultural fertilizer enhances plant growth. Again, this approach relies upon natural biodegradative processes that would occur anyway, but the rates of biodegradation are stimulated through human intervention. This approach to bioremediation can be very beneficial but it is not instantaneous—the environmental impact of an oil spill can be reduced from decades to years but the impact cannot be instantly or fully mitigated. It was this approach that was used to treat the Exxon Valdez oil spill.

2.1.2.3 Bioaugmentation: The final approach, termed bioaugmentation, involves the addition of living organisms or enzymes to augment naturally occurring biological populations. One of the concerns about bioaugmentation is the potential use of genetically modified microorganisms. Many groups are concerned about the potential impact of introducing genetically modified organisms into the environment. They view such organisms themselves as pollutants and have opposed their utilization for bioremediation. Environmental protection regulations do not preclude the use of genetically modified microorganisms but the regulatory frameworks are restrictive. Hence, while organisms have been engineered for enhanced biodegradative capacities, they have not been introduced for the purpose of bioremediation. Even if deployed, the introduction of genetically modified organisms would most likely have a localized effect, as most applications of bioremediation are intended for use at specific sites. Some approaches to bioaugmentation do not involve the degradation of the pollutant but rather its transformation or physical movement. Biotransformations can alter toxicity, solubility and volatility so that harmful substances can be detoxified, diluted, or removed from impacted ecosystems. In one approach, called phytoremediation, plants are used to extract pollutants from contaminated soils. While bioremediation per se should have no direct bearing on the subject of biological warfare, it should be recognized that the technology is based on the biodegradative properties of the microorganisms themselves.

3.0 Advances in analytical and vaccine technology

3.1 The very advances in biotechnology since the 1996 Review Conference that are cause for concern have also placed new capabilities in the hands of those conducting legitimate biological research. Though not without constraints, these same capabilities also make developing biological and toxin weapons much easier than developing adequate defense against them.

3.2 Vaccines: The development, implementation, and continued use of new vaccines depend on many factors. Although disease burden seems like an obvious quantitative measurement for setting priorities for new vaccine development and use, resources are not always allocated proportionately. Issues important to vaccine manufacturers, namely, production, intellectual property rights, product liability, and profit often balance public perception of the risks associated with a disease or vaccine. The explosive technological advances in the fields of immunology and molecular biology in the last 5 years have had an enormous impact on the identification of candidate vaccines against diseases.

3.2.1 Almost all vaccines in use today are of three types: live attenuated microorganisms, inactivated whole microorganisms, or split or subunit preparations. Each type has different strengths and weaknesses with respect to safety and efficacy. Traditional vaccine development methodologies have not yet led to the generation of a vaccine with all the characteristics required of the ideal vaccine, which is a major goal of biomedical sciences. The conventional approach to vaccine development requires cultivation of the pathogenic microorganism and its dissection using biochemical, immunological, and microbiological methods in order to identify the components important for immunity.

3.2.2 Genetic immunization, the use of DNA encoding antigens from pathogenic bacteria, viruses, and parasites is one approach. DNA vaccination entails administration of antigen-encoding DNA to direct synthesis of the antigen directly in the target organism. DNA vaccines afford numerous advantages over conventional vaccines, including ease of production, stability and transport. They overcome the need to cultivate dangerous infectious agents, and provide the possibility to vaccinate against multiple pathogens in a single shot. DNA vaccines are being developed for many pathogens of human and veterinary interest.

3.2.3 Complete genome sequences of microbes provide an inventory of genes encoding every virulence factor and potential immunogen. Vaccine development will benefit from emerging genomics technologies such as bioinformatics, proteomics and DNA microarrays. Genomic approaches allow prediction of all antigens, independent of their abundance and immunogenicity during infection, without the need to grow the pathogen *in vitro*. This allows vaccine development using non-conventional antigens and exploiting non-conventional parts of the immune system. Vaccine discovery starts *in silico* using genetic information rather than the pathogen itself.

3.3 Vaccine Delivery Systems: Proper stimulation of that part of the immune system found in the mucous membranes of the body is critical for effective protection against colonization and invasion of infectious agents. This requires administration of vaccine antigens directly to various mucosal sites. Genes are delivered as plasmid DNA (pDNA) or by viral vectors. There are new approaches for formulating and delivering pDNA and alphaviral replicon vectors, all of which have resulted in increased potency of gene-based vaccines. Controlled-release, microparticle, cationic lipid, viral, and bacterial delivery systems are being developed that afford some protection from environmental degradation and facilitate DNA uptake. The combination of sustained release and depot effect may reduce the amount of antigens or adjuvants needed to confer protective or sterile immunity. Other innovative approaches include vaccine production in plants. Researchers have already demonstrated induction of a virus-specific protective immune response to foot and mouth disease virus using a structural protein expressed in a transgenic plant.

3.3.1 Viral Tropisms: In addition to serving as vectors for vaccine antigens, viral particles can now be used to deliver nucleic acids as therapies. More importantly, viral tropisms can now be altered by expressing new or different fibers (ligands) on the outer surface of viral particles. In this way, the subpopulation of cells, which the virus attacks, can be changed or focused. Adenovirus vectors of this type are now in clinical trials.

3.4 While all of these technologies afford opportunity for dual-use, current trends in vaccinology and delivery systems suggest eventual reduction in the need to cultivate large quantities of dangerous infectious agents in order to produce vaccines, although such agents

will still be required for testing the safety and efficacy of vaccines. This could substantially reduce the importance, attached by some, of vaccine production facilities as potential sources of BW production and proliferation.

4.0 Other technological advances

4.1 Bioinformatics: The term bioinformatics is used to describe the application of information technology to the life sciences. While information technology has been applied to biology in the past, there are several emerging trends that are turning this into a large business: 1) the availability of large volumes of new genetic information; 2) advanced information processing capabilities; 3) the high market value of potential products created by this type of R&D; 4) availability of large amounts of venture capital; and, 5) the potential for shortening the time from discovery to market provided by the application of bioinformatics. In addition to creating scientific and commercial opportunities, these emerging technologies have also made it easier to create novel structures and substances from biomaterials.

4.1.1 Core information technologies that are having a fundamental impact on these processes include:

- (1) the dramatic reduction in the cost of memory allowing storage of large amounts of bioinformation on low cost platforms;
- (2) a suite of web-based technologies that has enabled worldwide distribution of biological and genetic information that is immediately available;
- (3) common data formats that allow integration of data streams from multiple sources;
- (4) novel methods for searching through these massive information stores allowing almost anyone to rapidly find core information for biomaterial design; and,
- (5) multi-dimensional visual analysis technologies. Such technologies enable a bio-designer to visually analyze huge amounts of biomaterials for evaluation and product design, not only analysis of sequences, but also all the data about the sequences and structures, functions, and properties of end products.

4.1.2 The first and most striking change in the last 5 years has been the amount of genetic information available worldwide. A simple search yields thousands of sequences with the amount of information growing by several orders of magnitude every few years. For example, today's capability to completely sequence a 3 million base-pair microbial genome in a single day at a high throughput sequencing facility, will, in 5 years, grow to sequencing a 20 to 30 million base-pair genome in a day. This will provide an avalanche of sequence information from which tens of thousands of new gene products will be discovered. This sequence information will come not only from microorganisms but other species as well. In considering the BW implications of the availability of this information, we must assume that researchers and others worldwide will be able to access basic DNA, protein, and functional informational resources.

4.1.3 Second, is the rapid increase in information technology that enables discovery of new constructs and their interrelationships to others on readily available low-cost computer equipment. While searching for portions of sequences used to be cumbersome, current technology allows searching, retrieving, and analyzing thousands of sequences within seconds. The process is multi-dimensional and can be steered by the individual through masses of

sequences. Visual analysis tools enable the most sophisticated, as well as lesser-trained individuals, incredible capabilities not seen heretofore in science.

4.1.4 These new analytical capabilities allow for rapid fusion of text information from thousands of scientific documents with genetic information. These capabilities fundamentally change the time of discovery compared to that of other disciplines. Time from inception of an idea to invention has gone from months/years to days/weeks. The knowledgeable biodesigner can now rapidly visualize relationships between hundreds of thousands of information units at one time.

4.1.5 The natural demand for improved health care, the demand for increased food production worldwide, the huge commercial potential, and reputation and wealth for those who can provide information and processes will encourage research using these technologies. This is in stark contrast to nuclear technology, which is usually highly restricted. We should expect major new developments in completely unconventional biological structures within the next 5 to 10 years.

4.1.6 These advances complicate the task of those seeking to limit their use for other than peaceful purposes. Assertive measures to control access to these resources for illicit purposes will likely reduce their availability and efficacy in addressing legitimate needs.

4.2 Microbial genomics: Since publication of the *Haemophilus influenzae* genome in 1995, the sequences of close to 30 microbial genomes have been completed during the past 5 years, and the sequences of more than 100 genomes, including several traditionally considered to be agents capable of being developed as biological weapons, should be completed within the next 2 to 4 years. The genome organization and gene content of the sequenced organisms has revealed incredible diversity. Nearly half of the information identified by these sequencing projects is for potential genes with no known biological function. The future challenge will be to determine function for the unknown genes. Soon, completed microbial genome sequences will represent a collection of greater than 200,000 predicted coding sequences. The explosion in genomic information has been driven by the availability of high-throughput nucleotide sequence determination technologies. The availability of numerous microbial genome sequences has profoundly altered our understanding of a number of fundamental biological processes. For example the enzymes involved in aminoacyl-tRNA (AA-tRNA) synthesis, a key process responsible for the accuracy of protein synthesis, have been found to be highly species-specific. In particular, a number of pathogens contain certain pathways of AA-tRNA synthesis that are unrelated to those found in their mammalian hosts. Since AA-tRNA synthesis is indispensable for cell viability, the discovery of pathogen-specific pathways and enzymes presents novel therapeutic and diagnostic targets.

4.2.1 In combination with assays of function, genomic-based approaches can facilitate efficient and directed research strategies to elucidate mechanisms of bacterial and viral pathogenicity. However, to take advantage of whole genome sequences, methods for production of gene products in surrogate hosts (heterologous expression) will be required that will work for large-scale, high-throughput gene expression. In addition, methods to test gene products for their potential as antimicrobial or vaccine candidates will be necessary for large-scale screening.

4.3 Toxicogenomics: Toxicogenomics is a sub-discipline of genomics that is particularly relevant to drug safety and combines bioinformatics with genomics to identify and characterize the mechanism of action of new drugs. Toxicogenomics can influence the drug development process by increasing the knowledge of toxic mechanisms; improving the understanding of model in vitro and in vivo systems; providing rapid screens for compound toxicity and better methods for monitoring clinical trials; and allowing easier, quicker identification of lead compounds and more informed decisions regarding safety and efficacy of compounds. Toxicogenomics can offer a better understanding of the relationship between genetic variability and individual response to pharmaceutical agents and help prevent deaths and burdens associated with post-marketing identification of hypersensitive sub-populations. Also the application of toxicogenomics may contribute to understanding the toxicity of relevant toxins at the genetic level.

4.4 Proteomics: The completed genome of an organism, from the smallest virus to a human or a blue whale, represents the source code for all the structural and working parts that comprise that organism. Each gene either determines one of these parts or regulates the expression of those parts. Characteristically, for every organism sequenced, from microbes to humans, about 50 percent of those parts perform functions or serve other roles that we do not yet understand. The 'post-genomic era' that confronts us already is proteomics. Proteomics is not only the systematic separation, cataloguing and study of all of the proteins produced in an organism, it is also the study of how proteins change structure during interactions with other proteins. Such structural changes enable the organism to do the varied things it does, and to ultimately give rise to disease or health in an organism. It is also the systematic characterization of those small molecules that can interact with proteins and initiate, terminate, or modulate what they do. Since its promise for drug discovery and the associated significant economic returns, proteomics is of great interest to biotechnology, computer and software companies around the world.

4.4.1 Presently, the number of genes in the human genome is estimated to range from about 30,000 to perhaps 60,000 depending on the algorithms that are used to search for them. Regardless of the number that is finally determined; the number of proteins that can be controlled by those genes is considerably larger, perhaps in the vicinity of 300,000 to 400,000. To add to this complexity, many if not most of the activities in a cell are carried out in sets of proteins organized into closely regulated pathways. There are three major proteomics technologies, 2-D gel electrophoresis, nuclear magnetic resonance imaging, and mass spectroscopy. In complementary areas, large-scale, high throughput structural genomics projects will provide vast libraries of the structures, and structural motifs, encoded in the genomes of microbes, humans, and many model organisms. The multi-disciplinary infrastructure required for these efforts will involve the use of high throughput protein production and crystallization and synchrotron radiation for structure determination on a large scale. Currently, there are five synchrotron radiation facilities in the U.S. six in Europe, and two in Asia that serve as international collaborative centers for protein crystallography and structural biology studies. Coupled with high performance computing and bioinformatics resources, the protein structural information will be combined with proteomics information to advance our understanding of structure-function relationships with enormous potential for discovery of innovative approaches to design and production of new and improved drugs and vaccines. To optimize their promise, powerful computational modeling and molecular simulation capabilities will be needed both to better predict protein function(s) given gene sequence data as well as to model small compounds that might bind to and affect function.

4.4.2 The most dramatic uses of proteomic technologies will be in medicine and human health. Further expected yields from genome research will include modified genes and microbes that may contribute to new energy sources, new industrial compounds and chemicals, microbes for environmental remediation, and a range of other industrial activities. These technologies also raise concerns regarding their misapplication for BW proliferation.

4.4.3 Science, particularly in the biological and genomic areas, has advanced at incredible speed during the last 5 years, in large measure due to the stimulus of the Human Genome Project and technologies for high throughput sequencing and protein characterization that it has enabled. While much remains to be learned, the technologies that have been recently developed permit much more detailed and high throughput elaboration of biological information than ever before. New computational capacities enable the query of these expanded biological databases, “mining” them for insights and useful information, to proceed faster than ever. Rapid advances in other enabling technologies such as high throughput micro scale automation and robotic systems will provide the infrastructure to reap the benefits of large-scale genomics and proteomics projects.

4.5 DNA shuffling: DNA shuffling is a powerful tool for directed molecular evolution that is used to accelerate the rate at which one can evolve genes. It is a method for *in vitro* homologous recombination of pools of selected genes by random fragmentation and polymerase chain reaction (PCR) reassembly. This produces a range of “progeny” genes whose fragments are reassembled in subtly different ways. The enzymes used in the reassembly process are also prone to errors, which introduce more point mutations, adding further to the genetic diversity. The progeny genes are then reintroduced into a host organism, such as bacteria, which are then selected to identify those with desired traits. This technique can be used to reassemble fragments taken from families of related genes from different organisms and has recently been employed to shuffle entire genomes in commercially important organisms. Single or multigene traits that require many mutations to express desired characteristics can be evolved rapidly. Application of DNA shuffling technology has been extended to small molecule pharmaceuticals, pharmaceutical proteins, gene therapy vehicles and transgenes, bacterial and viral vaccines, and laboratory animals.

4.6 DNA Microarrays: Complete genomic sequences for microbial pathogens and hosts offer sophisticated new strategies for studying host-pathogen interactions. DNA microarrays exploit primary sequence data to measure transcript levels and detect sequence polymorphisms, for every gene, simultaneously. The design and construction of a DNA microarray for any given microbial genome are straightforward. By monitoring microbial gene expression, one can predict the functions of uncharacterized genes, probe the physiologic adaptations made under various environmental conditions, identify virulence-associated genes, and test the effects of drugs. By using host gene microarrays, one can explore host response at the level of gene expression and provide a molecular description of the events that follow exposure. Host profiling might also identify gene expression signatures unique for pathogens, thus providing a novel tool for diagnosis, prognosis, and clinical management of infectious disease.

5.0 Outbreaks of infectious diseases

5.1 Predictions that infectious diseases would be eliminated as a major threat to human, animal and plant health have been shattered by emerging and reemerging infections. Prion diseases, arbovirus infections, hepatitis C, enterotoxigenic *Escherichia coli* infections, tuberculosis, and foot and mouth disease have provided alarming examples of emerging or

reemerging infectious diseases. The increasing resistance of many pathogens to antimicrobial agents is a major source of concern. The causes of the emergence or reemergence of infectious diseases are multiple and diverse, often in direct relation to human activities (population migrations, changes in husbandry or farming practices, worldwide commerce, inadequate or inappropriate uses of antibiotics) but also with climatic changes in several areas. Understanding the dynamics of emerging and reemerging infections is critical to efforts to reduce the morbidity and mortality of such infections, to establish policy related to preparedness for infectious threats, and for decisions on where to deploy limited resources to fight against infections.

5.2 Prion diseases: The Prion diseases pose unique scientific, medical, veterinary and regulatory challenges. The potential threats to public health posed, particularly; by bovine spongiform encephalopathy (BSE) and variant Creutzfeldt-Jakob disease (vCJD) are significant. Six years after the first reported cases of vCJD, there is still no clear indication of the magnitude of the primary epidemic, or of the likelihood of horizontal transmission of this untreatable disease by iatrogenic means, particularly by blood and blood products. All age groups appear to be susceptible to the vCJD strain of the agent derived from BSE cattle. BSE is associated with a transmissible agent, although the nature of the agent is still a matter of debate. The agent is highly stable and easy to produce and multiply. In the favored model of Prion replication, direct interaction between the pathogenic Prion protein template and endogenous cellular Prion protein is proposed to drive the formation of infectious prions. Feline spongiform encephalopathy, or Prion disease of cats, first reported in Great Britain in 1990, is also believed to result from the consumption of food contaminated by the agent of BSE. There are currently no reliable tests to detect pre-symptomatic disease in infected animals.

5.3 Foot and Mouth Disease: Foot-and-mouth disease (FMD) is the most contagious animal virus disease of cloven-hoofed livestock and requires reliable and accurate diagnosis for the implementation of measures to effectively control its spread. The FMD epidemic in Great Britain and other European Union countries highlights the devastating impact that naturally occurring diseases can have on the economies of affected countries. Knowledge of the factors that determine the transmission potential of the pathogen may be useful for planning biosecurity programs at the herd, regional, and national levels.

5.4 West Nile Fever Virus: West Nile fever emerged in New York State in the United States in 1999. The appearance of WNV in the United States and Canada was possibly due to animal transportation or migration. WNV is a flavivirus maintained in nature by a bird-mosquito cycle. Currently, no human or veterinary vaccine is available to prevent WN viral infection, and mosquito control is the only practical strategy to combat the spread of the disease. The experience with the WN virus outbreak offers practical lessons in outbreak detection, laboratory diagnosis, investigation, and response that might usefully influence planning for future disease outbreaks. Many of the strategies used to detect and respond to the WN virus outbreak resemble those that would be required to confront other serious infectious disease threats, such as pandemic influenza or bioterrorism.

6.0 Summary

6.1 Since the last Review Conference in 1996, remarkable progress has been made in the life sciences, particularly in the fields of genetic modification, genomics, proteomics, bioremediation, biocontrol agents, vaccine development and bioinformatics. The progress made in these areas of biotechnology has been enabled by parallel advances in other disciplines, especially, physics, chemistry, computational sciences, engineering sciences, and materials sciences, and is marked by large-scale, international collaborative efforts. While we cannot predict the future of the technologies referenced in this document; we can assume that most are relevant to the Biological and Toxin Weapons Convention (BWC).

6.2 The global availability of massive amounts of genomic information and capabilities to manipulate that information for both peaceful and non-peaceful purposes is both encouraging and unsettling. These technological achievements have implications for enhancing biological weapons proliferation, but they also provide mechanisms for enhancing protection and prophylaxis against such weapons, thereby strengthening the BWC. Some view BW as the WMD threat of the 21st century. It is important to note that application of these same technologies to biotechnology and vaccinology will likely provide a key to reducing the usefulness of BW weapons in the 21st century via creation of globally available protective measures such as new classes of antiinfectives, therapeutic products, and broad spectrum vaccines. Such capabilities could reduce the ability of a proliferator or terrorist to initiate and propagate disease in target populations, be they human, animal or plant.

6.3 Agroterrorism would be an available form of economic warfare. Thus, protection against animal and plant diseases is important to the global economy. This is underscored by the special reference to animals and plants contained in the 1996 Final Document of the Fourth Review Conference. It should also be noted that in the future, as advances in proteomics, bioinformatics and vaccinology mature and find industrial applications, the need for large-scale production of pathogens might decrease, reducing the likelihood that a proliferator with a bacteriologically-based program could conceal illicit activities in legitimate commercial facilities. The United States continues to believe that all of the scientific and technological developments described above are encompassed comprehensively under Article I of the BWC, which in turn places them within the purview of the Convention.
