The Royal Society

SCIENTIFIC ASPECTS OF CONTROL OF BIOLOGICAL WEAPONS

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SCIENTIFIC ASPECTS OF CONTROL OF BIOLOGICAL WEAPONS

Report of a Royal Society Study Group

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FOREWORD

Biological weapons have been a threat for many years but recent advances in biotechnology make the problem potentially more serious. Effective control through international agreement is an urgent necessity. Non-proliferation issues are complex and require the earnest attention of politicians, lawyers, scientists and indeed all who can make a constructive contribution.

In 1992 the Royal Society's Group on Scientific Aspects of International Security set up a small Study Group of Fellows to examine how science could contribute to the control of biological weapons. The Study Group, chaired by Professor Harry Smith CBE FRS, has considered the most recent developments, consulted widely among experts and has set down its thoughts and conclusions in this Report.

In April 1994 the Society's Council strongly endorsed the Report and recommended that it be circulated widely to organizations and individuals with an interest in biological weapons control. The Report breaks new ground and puts forward ideas on how international security in this important area can be enhanced.

On behalf of the Society I should like to express our thanks to the Leverhulme Trust for its generous financial support of this work.

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SUMMARY

1. BIOLOGICAL WEAPONS

Biological weapons (BW) are living, i.e. self-replicating, microorganisms which are intended to be spread deliberately in aerosols, food or water to cause disease or death in man, animals or plants. They are usually bacteria or viruses; anthrax bacilli and Venezuelan equine encephalitis virus are typical examples. The term BW is also used for toxins, non-living poisons of biological origin, which are either lethal like botulinum toxin or incapacitating like staphylococcus enterotoxin B. These four and about eight other agents were stockpiled for use as BW during the second world war and its aftermath. In the past two decades, the potential danger from BW has increased for two main reasons. First, the rapid progress of biotechnology and the advent of genetic manipulation have made it possible to produce many new agents. Second, as was emphasized by the Gulf War, BW are particularly attractive to some developing countries because they can be produced cheaply with relatively moderate facilities and be used in covert operations. The escalating dangers must be controlled.

2. PURPOSE OF THE STUDY

International efforts to control BW focus on the `Convention on the prohibition of the development, production and stockpiling of bacteriological (biological) and toxin weapons and on their destruction' (the BW Convention), which was opened in 1972, reviewed in 1980, 1986 and 1991 and has now been signed by over 115 nations. Many problems, notably those related to compliance with the obligations and verification, remain to be solved before effective control of BW is established. Some of these problems are scientific. The purpose of the study was to examine the scientific aspects of control of BW with a view to making suggestions as to how present measures might be improved.

3. APPROACH

A small Study Group of Fellows of the Royal Society was formed. They were experts in microbiology, genetics and other disciplines appertaining to BW but most of them had no previous knowledge of either BW or problems relating to their control; thus, they could provide a fresh approach to the subject. Five aspects of the BW Convention that might benefit from scientific input were identified: compass (definition of agents and hosts); compliance and confidence-building measures (CBMs); verification; technology transfer; and international scientific cooperation. Position papers on these subjects were discussed with government scientists and other experts invited from outside before the Group assessed the position and came to its own conclusions. These are set down in the Report after three introductory chapters.

4. NATURE AND TARGET OF THE REPORT

The Report is highly technical in some sections. It provides detailed information on important aspects of control of BW for those persons who are specifically interested in the measures being contemplated by signatories of the BW Convention.

The Report should be useful to government officials preparing for the 1996 Review of the Convention in which compliance and verification will be important issues. When the Chemical Weapons (CW) Convention, which will come into operation in 1995, is reviewed, the section on toxins of this Report (Chapter 4) should be taken into account. The comments on technology transfer (Chapter 7) may be of interest to government officials in any review of the current legislation on export control.

5. CONCLUSIONS AND RECOMMENDATIONS

The more important recommendations are in bold print.

5.1 Compass of the BW Convention: definition of agents and hosts

1. **Article I of the BW Convention defines BW agents. It is sufficiently comprehensive to cover both present BW and future developments. It should be retained with supporting protocols such as that which states it applies to human, animal and plant hosts.**
2. **Toxins are of increasing importance. They should be defined in a manner which is suitable for insertion in both the BW Convention and a revision of the CW Convention**.
3. To aid in the establishment of CBMs and verification procedures, some examples of live agents and toxins should be listed to illustrate the wide range available. Attempts to list all possible BW agents should be discouraged.
4. The scale on which the quantities of live agents and toxins are produced for peaceful purposes should be declared annually.

5.2 Compliance and CBMs

1. Signatories to the BW Convention have agreed to declare annually: high containment facilities and national biological defence programmes; unusual outbreaks of disease; national legislation appertaining to the BW Convention; past offensive and defensive programmes; and facilities for preparing human vaccines. Also, publication of results and contacts between staff are to be encouraged. A good response to these seven CBMs would increase trust between nations, and provide information on the location of high risk areas for verification purposes.
2. At present, the response is poor (about 30% of the signatories) and not improving. It must be increased otherwise the Convention will founder.
3. **The present voluntary system could be improved by establishing an administrative office to send out and chase in the reply forms and to analyse them for verification purposes. The establishment of such an office should be the highest priority for the 1996 Review. An extension of the secretariat of the CW Convention to cover this task has much to commend it.**
4. **The reply forms should be made simpler so they are more easily completed by developing countries. Only essential information should be requested including the name and address of the national agency(s) making the reply. Circulars should make clear that by completing the forms the government would receive copies of replies from all responders and a list of non responders.**
5. **If these improvements in the voluntary system do not succeed, the replies should be made mandatory.**

5.3 Scientific aspects of verification

1. **An ad Hoc Verification Group of Governmental Experts (VEREX), set up under the 1991 Review of the BW Convention, considers that verification should not rely on any one criterion but be multicomponent in nature. This view is endorsed.**
2. **The crux of detecting work on BW is identification of specific biological agents in circumstances that cannot be justified for legitimate purposes permitted by the Convention. Verification methods should concentrate on this point.**
3. On-site inspection of high risk areas is the best method of verification. The easiest way of identifying these areas is from intelligence sources and/or accurate replies to the CBMs, hence the crucial importance of improving these replies (see previous section). In the absence of such hard data, a combination of remote imagery and near-site (within 1km) spectroscopic and biochemical interrogation of gaseous exhausts and fluid effluents has potential for identifying biological facilities.
4. An essential requirement for verification is ability to detect unequivocally biological agents during on-site inspections, and near-site if the former are curtailed.
5. **Identification of all possible agents including those that might be produced by genetic engineering is not realistic in relation to effort and cost. The objective should be to reveal possible *intent to use BW* in the establishment under scrutiny by unequivocal detection of relatively few agents. At present these agents should be the 12 `classical agents' i.e. those weaponised in the past and most likely to be used by nations newly entering the field. The development of multiplex testing in the future could extend the range of agents detectable by the methods described below.**
6. **Two internationally validated identification methods capable of use at the site of inspection are needed for each agent Base laboratory investigations need to be conducted only when positive indications of BW activity are found.**
7. **Enzyme linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR) can detect agents at the levels of sensitivity required for on-site and near-site inspections. The simplest, cheapest and most effective method of providing unequivocal identification of all the classical agents in the immediate future (5-10 years) is the use of the ELISA and PCR by inspectors with portable equipment in basic facilities (power and water supplies, a bench and a sink) that are likely to be available at any location of inspection. This procedure is strongly recommended.**
8. If potential BW agents are identified by on-site inspections or their use is admitted in replies to CBMs, assessment of whether or not they are used in circumstances justified for legitimate purposes must be based on judging whether the facilities, the equipment, the records and information obtained by interviewing staff during on-site inspections, fit with the stated purpose of the establishment. Signs of large scale production might indicate BW activity.
9. **Special attention should be directed to detecting delivery systems such as munitions with special spreading devices and aircraft fitted with spraying equipment: also facilities for, or records of, large-scale aerosol experiments in chambers or the open air.**
10. Scientific aids are neutron activation analysis interrogation of closed containers, base laboratory virulence testing of suspicious strains of potential agents and X-ray examination of weapons for specialized detonators or spreading devices.

5.4 Technology transfer

l. The BW Convention attempts to prevent technology transfer in relation to aggressive purposes (Article Ill) and to encourage it for peaceful purposes (Article X). There is a conflict between the two because the knowledge and equipment are often the same for both. Rigid enforcement of Article III could hinder economic development in some nations.

2. On 31 December 1992, because of the increasing danger of proliferation, the UK Government enacted legislation to restrict export of BW related materials and is contemplating restriction of transfer of intangible technology.

3. Restriction of transfer of intangible technology would be undesirable because of its normal use in medicine and agriculture. Also, it is virtually impossible to accomplish. It would contravene Article X of the BW Convention and would hinder efforts to increase transparency between nations.

4. Restriction of transfer of seed cultures, large scale production equipment and containment facilities can, at best, achieve only a short delay (1-2 years) in development of BW with a risk of curtailing peaceful operations in developing countries.

5. Restriction of means of delivering and testing aerosol BW agents would prevent immediate acquisition and use of BW without repercussion on peaceful operations.

6. The UK Government cannot ignore the increased threat of proliferation but there may have been an over reaction in the present legislation with regard to both the number of countries affected and the items curtailed. A determined aggressor will obtain BW if he needs them. Only a short delay in proliferation is achievable. This delay could be attained more simply than the present legislation which is potentially inhibitory to the progress of developing nations. The restrictive measures should be concentrated on countries known to be interested in developing BW. Also, the lists of restricted items should be reduced and the ban on delivery systems emphasized.

5.5 International scientific cooperation

1. The present cooperation of international experts on verification issues should be extended. Mutual confidence and respect would follow and hence greater transparency.

2. If an international organization was established at the next Review Conference (1996) for the purposes of verification, its scope could be widened to investigate instances of alleged use of BW and, possibly, to render help in areas when BW had been used.

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1. INTRODUCTION

Biological weapons (BW) are living, i.e. self-replicating, microorganisms which are intended to be spread deliberately to cause disease or death in man, domestic animals or plants. They are usually bacteria or viruses. The term is also used for toxins, non-living poisons of biological origin which are either lethal or incapacitating. Examples of the former are anthrax bacilli and Venezuelan equine encephalitis virus; and of the latter, botulinum toxin and staphylococcus enterotoxin B; all four have been stockpiled for use as BW in the past. The potential danger from BW has increased in the past two decades for two main reasons. First, the advent and rapid progress of genetic manipulation has made it possible to produce new agents. Second BW are particularly attractive to some developing countries and terrorists because they can be produced cheaply and used for covert operations. The Gulf War raised public awareness of this particular aspect. The rapidly escalating danger must be controlled.

There has always been a widespread condemnation of BW and, after the first world war, the 1925 Geneva Protocol prohibited the use of bacteriological as well as chemical warfare. After the second world war, efforts continued in the United Nations to control BW as for all weapons of mass destruction. In 1972, the "Convention on the prohibition of the development, production and stockpiling of bacteriological (biological) and toxin weapons and on their destruction" (The BW Convention) was opened for signature. Over 115 nations have now signed it but the Convention had many flaws. Although there have been three reviews in 1980, 1986 and 1991 to improve it, many problems remain to be solved before effective control of BW is established. Some of the problems are political and administrative but others are scientific. This study is concerned primarily with the scientific problems.

The task was undertaken by a Study Group of the Royal Society's Group on the Scientific Aspects of International Security (SAIS Group). The SAIS Group was established by the Royal Society Council in 1988 with the following terms of reference:

To consider the scientific and technological aspects of international security and arms control and in particular to :

(a) undertake studies and prepare advice
(b) maintain contact with similar groups of scientists overseas
(c) provide briefing for Fellows
(d) report to Council

Subject to Council approval, the results of the studies will be made available to Government bodies such as the Foreign and Commonwealth Office (FCO) and they may be published in an appropriate manner by the Society. The Group's activities are completely open, strictly scientific and independent of Government. From the beginning, the SAIS Group has had close contact with a similar group of the National Academy of Sciences of the USA and, more recently, links have been formed at the highest level with other national academies through the Amaldi Conferences initiated by the Lincei Academy (Italy). At first, attention concentrated on control of conventional and nuclear arms. During 1991, however, the SAIS Group considered the draft Chemical Weapons (CW) Convention and, through the President of the Society, provided the FCO with scientific advice before the intensive international negotiations in September 1991 which led to the signing of the Convention in 1993. The present study is the first time the SATS Group has dealt with BW.

The study was financed by the Leverhulme Trust which provided funds for a part-time research assistant and clerical back-up.

1. THE POLICY OF THE STUDY: CONCENTRATION ON THE SCIENTIFIC ASPECTS

Much was written about BW and the BW Convention before the Gulf War and the 1991 Review Conference. They prompted a further spate of articles from knowledgeable individuals and organizations such as the Federation of American Scientists and the Stockholm International Peace Research Institute. References (1-10) to a selection of the articles are given at the end of the Report. In most cases the articles are concerned with the admittedly important, political and administrative aspects of the subject rather than the strictly scientific aspects. Experience in dealing with the FCO on the CW Convention (see above) has indicated that concentration on scientific aspects can be extremely helpful to diplomats who are experienced and expert in political and administrative matters but relatively naive over science, especially if it is intricate. Hence, the policy of the study has been to concentrate on the scientific aspects of BW control thereby filling a possible gap in knowledge available to conference negotiators. Some reference to political and administrative matters was unavoidable but it has been kept to the minimum.

An appropriate Study Group of the Royal Society's SATS Group is in a unique position to provide scientific advice at the highest level. In addition to members of the Study Group, there are many additional Fellows of the Royal Society with considerable knowledge of microbiology, genetics, biotechnology, immunology, toxicology and molecular biology, the disciplines that appertain to BW. This knowledge can be tapped at will by asking appropriate Fellows to join particular meetings of the Study Group. Furthermore, some Fellows of the Royal Society have contact with matters of defence and know other scientists both in the UK and overseas who can assist in the specific study of BW control.

2. THE OBJECTIVES

The broad objective was to study the scientific aspects of control of BW with a view to providing suggestions for improving the measures presently adopted by the UK Government and international authorities. Subject to approval by the Council of the Royal Society, the study would be published and be made available to the FCO. In preliminary discussions, the Study Group (from now on called the Group) identified five aspects of the BW Convention and subsequent reviews that might benefit from scientific input.

1 Compass of the BW Convention: definitions of agents and hosts.
1. Compliance and confidence building measures.
2. Scientific aspects of verification.
4. Technology transfer.
5. International scientific cooperation.

Elucidation of the science involved in these aspects was the specific objective of the study.

3. THE APPROACH

Most members of the Group were experts in microbiology, genetics and other disciplines appertaining to BW but they had no previous specific knowledge of either BW or problems relating to their control; thus they could provide a fresh approach to the subject. To provide the necessary background, experts (Appendix I) were invited from outside for discussions on the chosen topics before the Group assessed the position and came to their own conclusions. The consultation with experts began with a visit to the Chemical and Biological Defence Establishment at Porton Down where the Director General, Dr G.S. Pearson, and his staff provided background information on BW and their control; and also discussed with the Group all five aspects listed under the objectives. At subsequent meetings of the Group, one of the five aspects was discussed in detail with about three experts during a preliminary session: a position paper prepared by the research assistant and the chairman provided a focus for the discussion. A second session without the experts followed when the paper was considered in the light of the preliminary discussion and modified accordingly. After approval of the modified paper by the Group at its next meeting it formed the first draft of the relevant chapter of the Report. Finally, all the chapters were brought together with appropriate introductory chapters and conclusions into the full Report.

This Report is intended for those persons specifically interested in verification and other matters of control presently being contemplated by the international community.

2. BIOLOGICAL WEAPONS AND THE 1972 CONVENTION

Biological weapons (BW) including toxins were defined in the previous chapter. This chapter summarizes the history of their development and the first attempt in 1972 to control them specifically.

1. THE DEVELOPMENT OF BW

Throughout history, infectious diseases contracted naturally during war have exacted a high toll on human life e.g. yellow and typhoid fevers during the Caribbean and South African wars respectively. Also, some military commanders deliberately used infectious diseases as weapons of war well before they were known to be caused by microbes. Diseased bodies were catapulted into besieged cities, wells were poisoned with putrefying bodies and blankets from smallpox patients were distributed amongst American Indians (11,12). As soon as the microbial aetiology of disease was proved by Koch in 1876 and specific pathogenic bacteria were cultured artificially, the possibility of using them as weapons was apparent. Although feed contaminated with anthrax spores was used by the Germans to sabotage army horses in the first world war (11,12), it was not until the 1920s and 1930s that significant military interest in BW began (13).

In the 1930s, the Japanese had a large programme in Manchuria for developing BW which may have been used during their war with China (12). British interest began with an enquiry committee set up in 1936 by the Committee for Imperial Defence and much research and development occurred at Porton Down during the second world war (13). The feasibility of one BW, anthrax spores, was demonstrated by the trials on Gruinard Island and botulinum toxin was shown to kill animals by the aerosol route. Although a joint effort with the Americans and Canadians to develop an anthrax bomb did not materialize, cattle cake impregnated with anthrax spores was proved lethal to domestic animals and stockpiled for dropping over enemy territory, had retaliation been required for first use of BW by Germany (13). The stockpile was destroyed soon after the war (13). The British data provided the foundation for the subsequent US programme on BW which started at Fort Detrick, Maryland in 1943 and continued until 1970. The offensive programme was then terminated and the stockpiles of several live and toxin weapons including some aimed against crops were destroyed (7,13). The USSR never admitted to a BW programme but was considered to have one by Western governments especially after the 'Sverdlovsk' incident when a large outbreak of anthrax occurred near a Soviet biological facility (7). Recently the development of BW by the USSR has been admitted by Russian Government officials. Undoubtedly, other countries have had BW programmes and according to American sources about 10 nations are presently engaged in such operations (10). It is clear from United Nation inspections that a programme, at least at research level, was operating in Iraq (10). Also the break-up of the former Soviet Union has not helped the situation.

Research and development of BW during the second world war and its aftermath had clearly indicated that they were to be used against crops and domestic animals as well as men, and that toxins as well as live agents were part of the repertoire (1,2,14). Up to the 1970s, however, there were relatively few BW agents, not more than 20 in all: examples are anthrax, brucellosis and tularaemia bacilli, botulinum toxin, staphylococcus enterotoxin B and Venezuelan equine encephalitis virus (5). These agents can now be called the `classical agents'. Lateral thinking from the use of CW during the first world war prompted the view

that BW would be deployed only on the battlefield and by the aerosol route. The military have never been keen on BW, especially live agents (8). The fact that only small quantities were needed compared with CW was outweighed by the delayed action due to the need for multiplication in the victim which was considered a distinct disadvantage. Also, the vulnerability of BW to environmental conditions made them far less reliable than conventional weapons. Finally, if BW were released could the spread of disease be controlled? Summarizing the position of BW at the end of the 1960s, there were few of them, they were for battlefield use by the aerosol route and they were not favoured by the military.

Since 1970, the position has changed (4). Many new agents, targeted not only against man but also animals and plants, can now become available from rapid developments in the two arms of biotechnology, fermentation techniques and genetic manipulation. Genetic manipulation of viruses can make them more noxious e.g. the introduction of genes that code for toxins or antigenic variations (which can circumvent any immunity established to conventional virus strains). Bacteria can be made resistant to antibiotics and rendered more dangerous by introducing the genes for extra virulence determinants. Toxins, formerly available only in small quantities, e.g. snake venoms or human bioregulators, can be produced in large quantities for weaponisation by gene cloning and large-scale fermentation. In addition to this major impact of biotechnology on the threat from BW, the general advance of virology over the past 20 years has had an influence. Many viruses causing exotic, non-endemic (therefore more dangerous) diseases, such as haemorrhagic fevers can now be grown rapidly in sufficiently large quantities for weaponisation. Side by side with the advances in science, the international political situation has increased the possibility of covert use of BW either by terrorists or by small nations in pre-conflict situations. The oral route of administration, i.e. water contamination and food poisoning does not need the sophisticated means of delivery demanded by the aerosol route. It could, therefore, be especially attractive to small groups seeking to disrupt strategic centres. Also, the delayed effect of live agents, so much disliked by the military for battlefield use, would be an asset for covert activity allowing the perpetrators to escape before the effects were apparent. Dovetailing with these political points, scientific knowledge of food poisoning microbes and toxins causing diarrhoea and/or vomiting has increased enormously in the last 20 years. Coupled together, the scientific advances and the new political aspects have increased substantially the number and type of the live agents and toxins that might be used.

To sum up, the threat of BW has been present since the microbial aetiology of infectious disease was proved in the last century. It has increased significantly in the last 20 years and will increase even further as mankind continues to bend microbial activity to its will. The threat must not be allowed to materialize.

2. THE PRELIMINARIES TO THE 1972 BW CONVENTION

As early as 1899 and 1907, the use of poison and pathogenic agents in war had been condemned and prohibited in the internationally agreed Hague Conventions (7). Arising from the use of CW in the first world war, the Geneva Protocol of 1925 (Appendix II) prohibited the `use in war of asphyxiating, poisonous or other gases'. Also, on a Polish suggestion (13), it included `bacteriological methods of warfare' .Currently about 115 parties have signed the Protocol but some have retained the right to use CW or BW in retaliation for first use by others.

In 1968, the Eighteen-Nation Committee on Disarmament (ENDC) discussed the prohibition of both CW and BW but the UK and other Western counties thought that they should be treated separately for the following reasons: BW were of little military value; they had not been used in war; cheating on a BW ban would not give important advantages to the cheating party; and a ban on BW without intrusive verification or compliance could be concluded rapidly without serious risks. On the other hand, CW were significant militarily and had been used in war. Compliance with a CW ban would have, therefore, to be verified by intrusive measures and agreement on such methods was not politically feasible at the time (7). In 1969, the UK submitted to ENDC a draft treaty banning only BW. Following the termination of the US offensive programme on BW and destruction of agent stockpiles in 1970, the Conference of the Committee on Disarmament, the successor of ENDC, commended the text of an agreed treaty to the UN General Assembly in 1971. In April 1972 the BW Convention (full title see previous chapter and Appendix III) was opened for signature.

3. THE BW CONVENTION

The BW Convention (Appendix III) came into force in 1975 and, at present about 115 parties have signed it. It covers both live agents and toxins. There are 15 Articles, the most important of which are 1, 11, III, VIII and X. The Convention has many weaknesses and they have been subjected to detailed critical analysis in many recent articles (5-10). Only the main points are summarized here.

Article I prohibits the development, production, stockpiling or otherwise acquiring or retaining of microbial or other biological agents or toxins whatever their origin or method of production, of types or in quantities that have no justification for prophylactic, protective or other peaceful purposes. There is a similar statement on weapons and methods of delivery. The definition is set wide which may have advantages as regards future developments. The phrase 'whatever their origin or method of production' allows for developments in biotechnology. On the other hand, the lack of definition of agents could lead to ambiguity in any compliance or verification procedures. Also, the actual quantities of agents that can be produced for peaceful purposes are not specified, again a source of complication in verification measures. An important omission was that research on BW was not restricted by this or any other Article.

Article II requires the destruction or diversion to peaceful purposes of all agents, toxins and weapons in a manner safe to populations and harmless to the environment. The timescale specified is within 9 months. This is completely inadequate for such a complex and dangerous operation as recent observations on destruction of CW have shown (10).

Article III prohibits transfer of agents, weapons or BW technology to other parties. There is potential conflict between this Article and Article X which requires the fullest possible exchange of equipment, materials and technological information for the use of bacteriological (biological) agents and toxins for peaceful purposes. In particular cases, it might be impossible to distinguish between peaceful and warlike purposes.

Article VIII states that nothing in the BW Convention shall be interpreted as in any way limiting or detracting from the obligations assumed by any State under the 1925 Geneva Protocol. Although it is difficult to see how a State that is complying with Article I of the BW Convention can use BW in war, such us is not specifically prohibited by the BW Convention. A state is only bound in this respect if it has signed unreservedly the 1925 Geneva Protocol (which bans the *use* of BW). As mentioned before, in signing the Protocol, some states have reserved the right to use BW in retaliation for first use by others.

3.1 The major deficiencies of the BW Convention

The major deficiencies of the original BW Convention were that there was no requirement for producing evidence of compliance and no provision was made for verification of Convention obligations by international assessors. These and the previously mentioned deficiencies were addressed in the three Reviews of the Convention which are the subject of the next chapter.

Finally, it should be stressed that the developing danger of use of BW by terrorists (see above) is not covered at present by the BW Convention which together with the Geneva Protocol is concerned only with the possible use of BW in *wars between nations.* At present, dealing with terrorist activity is regarded as an internal national matter. Similarly, possible use of BW for 'preserving internal security', as happened for CW in the case of the Kurdish population in Iraq, would be considered an internal matter. There are however, increasing signs that the United Nations is prepared to take action on internal national matters if the situation is sufficiently serious. Hence some extension of the BW Convention that will require from signatories control of the possible use of BW by terrorists within their countries and a ban on its use for internal security could be a subject for future negotiations on the BW Convention. This is however, a political matter not a scientific one.

3. THE 1980, 1986 AND 1991 REVIEWS OF THE BW CONVENTION

Although a step in the right direction, the 1972 Convention was unsatisfactory for the reasons given in the previous chapter particularly those related to compliance and verification. Since the original Convention there have been three attempts to improve on it.

1. THE 1980 REVIEW

The first review produced little change. The increasing influence on the threat of advances in biotechnology, particularly genetic engineering, was noted but all agreed that Article I was sufficiently comprehensive to cover recent scientific developments relevant to the Convention (7). Verification and complaints procedures were discussed as was cooperation in the peaceful uses of biological agents and toxins but in both cases there was no agreement on what measures should be taken (7).

At the same time as the first Review (March 1980) and soon afterwards (September 1981), confidence in the BW Convention was shaken by the `Sverdlovsk' and `Yellow rain' incidents respectively (7,15). In the first case, an outbreak of anthrax near the city of Sverdlovsk (900 miles east of Moscow) in 1979 was claimed by the USA to have occurred from the airborne release of anthrax spores from a Soviet biological facility run in contravention of the BW Convention: the Soviet Union said it resulted from marketing contaminated meat in violation of veterinary regulations (7,15). In the second case, the USA accused the Soviet Union of instigating the use of trichothecene mycotoxins in Laos, Kampuchea and Afghanistan and this was rejected by the Soviet Union (7,15). These allegations were neither proved nor disproved. They highlighted the weaknesses of the BW Convention regarding, compliance, verification and measures for investigating alleged outbreaks. Although the two cases spoiled superpower relationships at the time, they may have strengthened the feeling amongst signatories that the BW Convention must be improved at the next Review.

2. THE 1986 REVIEW

The second Review brought more progress (7). The concern of the impact of rapid developments in biotechnology, expressed at the first Review, had become stronger. There was much discussion on this point especially the increased threat from toxins. In the end, the general view was that Article I of the Convention was comprehensive enough to cover the recent developments. The final declaration stated that the Convention `unequivocally applies to all natural or artificially created microbial or other biological agents or toxins whatever their origin or method of production' and that `consequently, toxins (both proteinaceous and non proteinaceous) of a microbial, animal or vegetable nature and their synthetically produced analogues are covered.' The problem of defining BW was emerging.

There were abortive discussions about verification and complaints procedures which resulted in only a small improvement of the agreed procedure under Article V (see Appendix III). In the event of problems arising in relation to the Convention, any party might request a consultative meeting at expert level open to all parties. The meeting should be convened promptly, clarify any matter considered ambiguous or unresolved and suggest procedures for solving the problem (7).

Cooperation in the peaceful uses of biological agents and toxins was discussed, but despite efforts on behalf of the developing countries to set up an institution for such purposes, no concrete steps were taken (7).

The main advance was the introduction of four CBMs. These were to be undertaken voluntarily to increase the transparency of activities involving live agents and toxins. The CBMs were:

A. Annual provision of data on high containment facilities designed for work on dangerous biological materials.
B. Annual notification of outbreaks of unusual diseases.
C. Encouragement of publication of results of biological research related to the BW convention.
D. Promotion of contact between scientists engaged on such research including exchanges of staff for joint research.

The data were to be sent to the UN Department of Disarmament Affairs.

Finally, the Review underlined the importance of establishing national regulations to implement the Convention.

Unfortunately, the response to the CBMs was poor (7). Exchange of information should have commenced in 1987 and continued on an annual basis. Up to March 1991, although most developed countries had participated in one or more of the four rounds of declarations, about two-thirds of the 115 or so signatories of the Convention had not. Most of the developing countries had not sent in declarations, and in some cases the information provided was incomplete and of poor quality (7). In addition, few signatories (only 40 out of 117) had adopted national legislative or administrative measures to implement it (7).

3. THE 1991 REVIEW

The third and most recent Review was heralded by much writing and debate by both governmental and non-governmental agencies (5,6,7,9). The Gulf War added impetus to an already burgeoning concern about the increased threat from BW (about 10 nations were thought to be interested in BW). Proposals for the Review were numerous and complex. Only a few of them were adopted but the outcome of the Review was reasonably satisfactory. The BW Convention has been strengthened by agreement on the following measures (16,17).

Under Article I, live agents and toxins harmful to animals and plants are now covered as well as those affecting man. Also, there was a strengthening of the old CBMs (A,B,C and D) and the addition of three new CBMs (E,F,G).

A. Declaration of data on national biological defence programmes and facilities as well as high containment facilities.
B. Better definition of an unusual outbreak of disease.
C. Publication of results was emphasized.
D. Contacts between staff will be promoted and publicized.
E. Declaration of legislation and other regulations to implement the provisions of the Convention and to control the export of agents.
F. Past activities in offensive or defensive biological programmes since 1 January 1946 will be declared.
G. Production facilities for vaccines against human diseases will be declared.

In addition, annual explicit statements are required of nothing to declare, or nothing new to declare.

Finally and importantly, an ad Hoc Group of Government Experts (VEREX), open to all parties to the Convention, was established to identify and examine potential verification measures from a scientific and technical standpoint. The Group's mandate is to identify measures that could determine whether a State is contravening the Convention, taking into account the broad range of types and quantities of agents capable of being used for warfare. The measures should be judged against the following criteria: their strengths and weaknesses based on, but not limited to, the amount and quality of information they provide or fail to provide; their ability to differentiate between prohibited and permitted activities; their technology, material, man power and equipment requirements; their financial, legal, safety and organizational implications; and their impact on scientific research, scientific cooperation, industrial development, and confidentiality of commercial proprietary information. The ad hoc Group met in April and December 1992 and was asked to complete its work by the end of 1993 well before the next Review in 1996. At last, the nettle of verification had been grasped.

The major remaining weaknesses were first, the failure to establish firmly an administrative office, however small, to review annual returns on the CBMs and to chase non-reporting nations. Second, there was failure to set up an interim body to oversee the BW Convention between the five-yearly Reviews. Requests were made to the Secretary General to allocate staff and resources in Geneva to run the affairs of the Convention especially returns on CBMs but they are unlikely to materialize.

4. COMPASS OF THE BW CONVENTION:DEFINITIONS OF AGENTS AND HOSTS

The BW Convention was opened for signature in 1972. As was made clear by Chapter 2, there has been a vast increase in knowledge on microorganisms since the signing of the Convention, particularly on viruses. This has also been the case with toxins, especially those involved in food poisoning. Genetic manipulation is now a routine procedure in biological research and in large-scale production of biologicial materials. Future developments will be prodigious. It might be possible, for example, to produce binary biological weapons by combining a system that could donate new virulence determinant genes with a non-pathogenic potential recipient. The latter would become pathogenic once the virulence determinent has been transferred. Separate non-toxic components of multicomponent toxins such as the anthrax toxin are another possibility for a binary weapon. The present definitions in the Convention must be scrutinized, therefore, to see if they are adequate to cover the scientific advances that have already occurred and those that might happen in the future. Another point should be borne in mind in relation to definitions: increasing attention is to be given by the Convention signatories to CBMs and to methods for verification. A change or amplification of the present definitions may be required for these purposes. These matters are discussed in this chapter and some modifications are suggested.

1. THE PRESENT SITUATION

Article I of the Convention states:

> *Each State Party to this Convention undertakes never in any circumstances to develop, produce, stockpile or otherwise acquire or retain:*
>
> 1. *Microbial or other biological agents, or toxins whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes;*
> 2. *Weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict.*

As described in Chapter 3, these definitions were not changed in the three Reviews of the BW Convention. In summary, the increasing threat of advances in biotechnology, particularly genetic manipulation, was noted in the 1980 Review but all signatories agreed that Article I was sufficiently comprehensive to cover the recent scientific developments. In 1986, concern with the impact of developments in biotechnology was stronger and the increased threat from toxins also received special attention. In the end, however, there was general agreement not to change Article I. Regarding toxins, the final declaration stated that the Convention 'unequivocally applies to all natural or artificially created microbial or other biological agents or toxins whatever their origin or method of production' and that 'consequently, toxins (both proteinaceous and non proteinaceous) of a microbial, animal or vegetable nature and their synthetically produced analogues are covered'. It was the same in 1991, there was no change in the definitions of agents. However, the position on the hosts they might affect was clarified by stating categorically that the definition applied to agents affecting animals and food plants as well as man.

1.1 The position of toxins

As stated above, toxins are covered by the BW Convention. They are also covered by the CW Convention which was opened for signature in January 1993 and comes into force in 1995. The reference to toxins in the CW Convention is brief and inadequate in relation to their growing importance as weapons. There is no general description of toxins at any point, but only a mention of saxitoxin and ricin in annex I, schedule 1. This schedule lists many other chemical agents in addition to the two toxins.

1.2 Quantities of agents

Neither the original Convention nor the three Reviews specified the quantities of agents that can be produced for peaceful purposes.

2. THE FUTURE: PROPOSED ADDENDA TO ARTICLE I

Article I of the BW Convention (see above) contains definitions of agents (part 1) and of weapons (part 2). Only the definition of agents has been questioned as regards adequacy in the light of rapid scientific advances. The one on weapons has received little attention and is considered satisfactory. It should be emphasized however, that as pointed out in Chapter 2, it does not apply to use of BW by terrorists or for 'internal security'.

The advantage of a broad definition of BW agents is that it not only deals with the present situation but it is likely to cover future developments. Three Reviews of the Convention have concluded that the definition in part 1 of Article I - viz microbial and other biological agents or toxins whatever their origin or method of production - is sufficiently comprehensive for these purposes. The last Review emphasized that it applies to agents affecting animals and food plants as well as man. After considering recent advances in science and possible future developments such as binary biological weapons, these conclusions are fully endorsed by the Royal Society Group.

Against this background of retaining the present definitions in Article 1, the Group suggest three addenda to the definitions which might be incorporated during the 1996 Review of the BW Convention. The addenda and reasons for them are discussed in turn.

2.1 A definition of toxins that could also be incorporated in any revision of the CW Convention

A possible definition of toxins might read:

> *Toxins are lethal or incapacitating substances of biological origin that are active at less than 1 mg per kg. They may be produced either from natural organisms, or by transfer of appropriate genes into suitable vectors or by modification of known toxins or precursors or by chemical processes.*

It seems sensible to use the same definition of toxins for both the BW and CW Conventions so that no ambiguity can occur in interpreting the definition for different purposes. The position on toxins could be rectified at the next reviews of both the BW and CW Conventions.

2.2 A list of examples of live agents and toxins for use in CBMs and verification procedures

The broad definition in Article I covers all possible agents and toxins. Some specification of agents may be needed for purposes of checking compliance on CBMs and for establishing procedures for verification. It is not possible to cover all live agents and toxins which have a potential for use as BW. Many microbes harmful to man can be found in WHO lists of

Risk Groups II, III and IV (18). Similarly, many of those active against food animals and plants are provided in other publications (19). Furthermore, the microorganisms and toxins that either have been or could be used as BW have been published by several organizations (1-5). It would be unwise, however, to think that any of these lists contain all potential BW agents. Attempts to set down all live agents and toxins is not worthwhile; the list would be cumbersome, almost certainly incomplete and need continual updating as new microorganisms and toxins were discovered or created.

The aim should be to provide some examples of the many different types of agents that either exist now or might be produced in the future.

A proposed list of examples of live agents and toxins is given in Table I. Important in these examples are those agents that have been weaponised in the past: they are marked with an asterisk. It is probable that one or more of these agents would be forerunners in any programme contemplated by potential transgressors of the BW Convention, because developing them would offer the best chance of success as well as providing the required experience in a new field. They are therefore, the prime targets for verification measures. The examples also include a few of the possible vectors that might be used for genetically engineering new agents.

2.3 A requirement for declaration of quantities of agents used for peaceful purposes

Article I allows the production of agents or toxins in quantities that can be justified for prophylactic, protective or other peaceful purposes. Agreed limits of production might be helpful for fulfilling CBMs and for verification purposes. The Royal Society Group has considered the practical aspects of establishing such limits and ensuring compliance. Even if only those examples listed in Table I are considered, the number of agents is large. Each agent would have a different limit and such limits would have to be set in terms of numbers of lethal doses. These lethal doses are difficult to determine for live agents and those for animal models are not necessarily the same as those for man. Furthermore, experiments on animals are restricted in some countries. Even if limits could be set and verified, fixing the levels for particular countries would be difficult because of the differing needs. The Group, therefore, concluded that it would not be sustainable to set limits on quantities. On the other hand, the present situation where no information is available on the quantities produced for legitimate purposes is not satisfactory. It is suggested that signatories are asked to make an annual declaration of the agents and toxins produced, the quantities (numbers for live agents; weight for toxins) and their purpose. This would need an additional CBM.

3. SUMMARY OF CONCLUSIONS

I. Article I of the BW Convention is sufficiently comprehensive to cover present BW and future developments. It should be retained with some supporting protocols.
2. Toxins should be defined in a manner which is suitable for insertion in both the B W Convention and in any future revision of the CW Convention.
3. Some examples of live agents and toxins should be listed to illustrate the wide range available and to aid the establishment of CBMs and verification procedures. Attempts to list all possible BW agents should be discouraged.
4. There should be annual declarations of the quantities of agents and toxins produced for peaceful purposes.

Table I: Examples of live agents and toxins that could be used as biological weapons (BW)

The aim is to provide some examples of the many different types of agents that either exist now or might be produced in the future. Important in these examples are those agents that have been weaponised in the past. They are marked with an asterisk.

Naturally occurring harmful microorganisms (pathogens)

Active against man

Bacteria	**Bacillus anthracis* (anthrax)
	**Yersinia (Pasteurella) pestis* (plague)
	**Francisella tularensis* (tularemia)
	Vibrio cholerae (cholera)
Viruses	*Venezuelan equine encephalitis virus
	Tick borne (Russian Spring-Summer) encephalitis virus
	Congo-Crimean haemorrhagic fever virus
Rickettsia	* *Coxiella burnetii* (Q fever)
	Rickettsia rickettsii (Spotted Mountain Fever)
Fungi	*Coccidioides immitis*

Active against food animals

Bacteria	**Bacillus anthracia*
	Mycoplasma mycoides (pleuropneumonia)
	Brucella spp
Viruses	Rinderpest virus
	Newcastle disease virus
	African swine fever virus

Active against plants

Bacteria	*Erwinia cartovora* (potato rot)
Viruses	Necrotic yellow vein virus (beet)
Fungi	**Puccinia graminis* (cereal rust)
	**Piricularia oryzae* (rice blast)
	Erysiphi graminis (barley mildew)

Genetically manipulated natural pathogens

Pathogens such as the above examples genetically manipulated to make them more dangerous e.g. by induction of resistance to drugs or fungicides, by induction of antigenic change to circumvent natural immunity or that induced by vaccines, and by introduction of additional determinants of pathogenicity such as toxins (see below).

Table I (continued)

Vehicles for production of new agents by genetic manipulation

Live microorganisms, not necessarily pathogenic themselves, that are capable of genetic manipulation to introduce determinants of pathogenicity such as toxins (see below) so that completely new agents are produced.

Active against man and/or food animals

Bacteria	*Salmonella typhimurium* *Pseudomonas aeruginosa*
Viruses	Vaccinia virus Adenoviruses Capripox virus Fowl pox virus

Toxins active against man and animals

Source	
Bacteria	*Botulinum toxin A (Also, 7 other serotypes) *Staphylococcus enterotoxin B *Clostridium perfringens* alpha toxin
Fungi	Tricothecene Aflatoxin
Algae	Microcystin Anatoxin
Dinoflagellates	Saxitoxin Brevitoxin
Plants	*Ricin Abrin Monensin
Animals	Snake venoms Snail conotoxin Human bioregulators in abnormal amounts

5. COMPLIANCE AND CONFIDENCE-BUILDING MEASURES (CBMs)

The major deficiencies of the original 1972 BW Convention were lack of a requirement for producing evidence of compliance with its obligations and the absence of provision for verification. Although these deficiencies were recognized in the first Review (1980), little was done about them until the second (1986) and third (1991) Reviews when some sensible proposals for correcting the deficiencies were adopted (see Chapter 3). This chapter deals only with the measures related to compliance. Verification is considered in the next chapter but it is important to stress here that the two aspects are very closely connected. The main advance on compliance has been the voluntary undertaking by signatories of CBMs (see Chapter 3).

1. THE PRESENT SITUATION

1.1 The seven CBMs

The CBMs were outlined in Chapter 3. Fuller descriptions are as follows:

A. Annual declarations of data relevant to the Convention (location, scope and general description of activities). Information is required on research centres and laboratories that either meet very high national or international safety standards for handling biological materials that pose a high individual and community risk, or specialize in permitted biological activities directly related to the Convention. Also, annual declaration of data on national biological defence programmes and facilities is needed.
B. Annual declaration of all outbreaks of infectious diseases and similar occurrences caused by toxins that seem to deviate from the normal pattern as regards type, development, place or time of occurrence. Criteria for judging an unusual outbreak of disease were provided.
C. Encouragement of publication of results of biological research directly related to the Convention in scientific journals generally available to signatory States, as well as promotion of use for permitted purposes of knowledge gained in this research.
D. Active promotion of contacts between scientists engaged in biological research directly related to the Convention, including exchanges for joint research on a mutually agreed basis. Contacts between staff will be publicised by signatory States including information on exchange visits.
E. States should declare what legislation and other regulations they have enacted both to implement the provisions of the Convention and to control the export and import of agents, deleterious to man, animals and plants.
F. States should declare past defensive and offensive programmes since 1 January 1946. It is realized that such declarations may founder on security requirements, especially if specific agents and weapons are to be named, but more general declarations may be attainable.
G. States should declare production facilities which can be used for vaccines.

The forms that are provided for the annual declarations on the CBMs are shown in Appendix IV. Some are complex (e.g. Form A) and others vague (e.g. Form G).

1.2 The dual function of replies to CBMs

The original aim of the CBMs was to increase the transparency of activities related to BW in the hope that this would gradually build up trust between nations. This in turn would lead to greater confidence in the BW Convention as a means of preventing proliferation and use of BW amongst all the State signatories. This is still a major function of the CBMs but another has emerged as equally important. Verification is now being taken seriously by the State signatories as evidenced by the activities of VEREX set up by the 1991 Review (see Chapters 3 and 6). In any verification procedure, it will be essential to identify the high risk areas i.e. laboratories of high containment, facilities for national defence programme and vaccine production plants. The easiest way to accomplish this basic step is to use information derived from replies to the CBMs particularly A B C F and G. Without this information, the task of verification is much harder (see Chapter 6).

1.3 Poor response to CBMs

It was hoped that the number of annual declarations on CBMs would be substantial at the beginning of the scheme and increase over time leading to a build up of confidence in the Convention. This would be especially so if the information provided was consistently confirmed by any verification measures that might be agreed later on. Unfortunately, the initial response was not substantial and has not increased significantly since 1987 (see Appendix V). The situation did not improve after the 1991 Review. The figures for 1991 and 1992 (Appendix V) show that: the responders are still only about one third of the total number of State signatories; developing nations predominated amongst the non-responders; and some nations providing replies in 1991 had not done so in 1992. The last point indicates that nations may be becoming disillusioned after the initial impetus derived from the Gulf War.

The number of signatories (40) that have adopted national legislative or administrative measures to implement the BW Convention is equally disappointing.

2. FUTURE DEVELOPMENTS

Clearly, the situation on CBMs is unsatisfactory. The level of response must be raised otherwise the BW Convention will founder. Apart from the effect of continuation of the poor response on confidence building, attempts to establish verification measures without basic information on high risk areas are bound to fail.

The aim is participation by all signatories or, at least, the great majority of them. Only then can mistrust be halted in areas of greatest suspicion. Also, non signatories would have an incentive to join the Convention if they saw evidence that other nations considered it worthwhile, not the least because they could learn from the replies that were circulated to all responders. Until a better response is achieved for the present seven CBMs there is no point in adding more CBMs to the list, however desirable they may be, such as those set down by the Federation of American Scientists (5,6).

2.1 Measures to improve the level of response to CBMs

The only real solution to the problem is to make replies to CBMs mandatory as for the CW Convention. This will need a major reappraisal of the BW Convention. Until this is achieved, two measures could raise the level of response under the present voluntary system.

2.1.1. Establish an administrative office to oversee the CBMs. One major function of such an office would be to send out the forms for replies to CBMs regularly, to ask for replies by a fixed deadline and to chase non-reporting signatories. This would almost certainly raise the level of response. However, receiving and filing the replies would not be enough. Analytical staff would be needed to sift and correlate the information in relation to laying a basis for verification. This would entail contact with outside bodies e.g. the WHO when assessing whether or not an outbreak of disease was unusual. Other functions of the office would be to receive and collate intelligence information if it became available, to monitor publications relevant to work on BW (CBM,C) and to receive and analyse information on exchange visits between staff of appropriate institutes (CBM,D). An important function would be to advise the relevant offices of developing nations on filling in the reply forms for CBMs. Finally, circulation of all the responses to all responders, an important aspect of the confidence building operation, would be a function of the office.

A technical secretariat similar to that being set up for the CW Convention would be needed to accomplish all the tasks described above. It would be expensive though less so than for the CW Convention. The aim should be to set up as soon as possible an office capable of dealing with the most important of the functions outlined above; advice to developing nations on filling in the forms, chasing in of non-responders, identifying high risk areas for verification and circulating the responses to all responders. Expansion of the activities of the office could then progress as more demands were made e.g. for verification, measures, and more finance became available. Despite a request for such an office being high on the list of priorities at the Third Review nothing has materialized. The Secretary General has not yet allocated staff and resources in Geneva to run the affairs of the BW Convention. The establishment of an administrative office must be at the top of the list of priorities for the 1996 Review. Without it, the BW Convention will remain ineffectual. An idea worth exploring would be to extend the secretariat now established for the CW Convention to take care of this essential aspect of the BW Convention.

2.1.2 Make the annual declarations simple. Many signatories of the Convention do not have the scientific and administrative infrastructures enjoyed by the more developed countries that formulate the CBMs and design the annual report forms. It may be difficult for the less developed countries to provide detailed information on some points however desirable that information may be to give the complete picture. The aim should be to obtain some information from all at the risk of not gaining full information from some. Asking for too much information may discourage less endowed nations from returning the forms. Also, it may discourage commercial firms in more developed countries from cooperating with the BW Convention. This cooperation is essential if verification procedures are to be successful. The biotechnology industry is used to providing information under legislation covering health, safety and working conditions. Provided the information required by the BW Convention is simple and reasonable they will cooperate. The cardinal requirements are clarity and simplicity in the requests for information. The name and address of the national agency(s) making the reply is important. Only essential information (e.g. under CBM A names of agents and work on delivery systems in defence programmes) should be requested with minimal documentation on simple standard forms. The forms should be sent out and received back within a fixed timetable and the circulars should make clear that by completing the forms the governments would receive copies of replies from all responders and a list of non-responders. The replies should provide the complete information on each CBM as it existed on a fixed date (say January 1st) of the year in question. They should not be supplements or deletions from what had been said previously because this will make it

difficult to judge the present situation. The form which provides the overall declaration on all CBMs is the most important form. It is probable that the majority of developing nations will have nothing to declare and therefore, for them it will be a simple matter of completing one form.

Appendix VI contains drafts of forms that are far simpler than those currently used (Appendix IV). These forms may be found deficient in some points of detail but they are provided to establish the principle of making the demands of the BW Convention simpler.

3. SUMMARY OF CONCLUSIONS

1. Replies to the present seven CBMs are essential to increase transparency thereby building up trust between nations; and to provide basic information for verification purposes.
2. At present, the response (about 30% of signatories) is poor and not improving. Most developing countries do not reply.
3. The response must be improved substantially otherwise the BW Convention will founder.
4. To solve the problem, replies to the CBMs should be mandatory not voluntary; this requires a major appraisal of the BW Convention.
5. The situation could be improved by establishing an administrative office to carry out various functions related to the CBMs, especially chasing in and analysing the reply forms. The establishment of such an office should be the highest priority for the 1996 Review. An extension of the secretariat of the CW Convention to cover this task has much to commend it.
6. Responses could also be improved by making the reply forms simpler so they are more easily completed by developing nations. Only essential information should be requested including the names and addresses of national agencies making the replies. When the forms are circulated it should be made clear that by completing the forms, the governments would receive copies of replies from all responders and a list of non-responders.

6. SCIENTIFIC ASPECTS OF VERIFICATION

The previous chapter dealt with CBMs which were introduced in the second (1986) and third (1991) Reviews of the 1972 BW Convention in attempts to correct one of the two major deficiencies of the original Convention, lack of requirement for producing evidence of compliance with its obligations. This chapter considers measures to rectify the other deficiency, no provision for verification of the obligations. This matter was addressed for the first time in the third (1991) Review when VEREX was established.

1. INTRODUCTION

VEREX was asked by the 3rd Review Conference to identify, by the end of 1993, measures which could determine:

> *Whether a State Party is developing, producing, stockpiling, acquiring or retaining microbial or other biological agents or toxins of types and in quantities that have no justification for prophylactic, protective or peaceful purposes.*
>
> *Whether a State Party is developing, producing, stockpiling, acquiring or retaining weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict.*

The potential verification measures should be examined in terms of the following criteria:

1. Their strengths and weaknesses based on, but not limited to, the amount and quality of information they provide and fail to provide.
2. Their ability to differentiate between prohibited and permitted activities.
3. Their ability to resolve ambiguities about compliance.
4. Their technology, material, manpower and equipment requirements.
5. Their financial, legal, safety and organizational requirements.
6. Their impact on scientific research, scientific cooperation, industrial development and other permitted activities and their implications for the confidentiality of commercial proprietary information.

The terms of reference of VEREX require the measures to be considered from a purely scientific and technical viewpoint. The generation of any verification regime will be a formidable task which involves administrative, political, legal and financial matters as well as science and technology. These additional aspects are outside the remit of VEREX and will be addressed in a subsequent special conference. The mandate of VEREX also states that measures could be considered singly and in combination. Table 1 (from the December 1992 summary of the Ad Hoc Group's work) shows the measures identified for consideration.

Table 1: List of Potential Verification Measures

I. Off-Site Measures

1. Information monitoring
- 1.1 Surveillance of publications
- 1.2 Surveillance of legislation
- 1.3 Data on transfers and transfer requests and on production
- 1.4 Multilateral information sharing
- 1.5 Exchange visits

2. Declarations
- 2.1 Declarations (including notifications, data on transfers and transfer requests and on production)

3. Remote sensing
- 3.1 Surveillance by satellite
- 3.2 Surveillance by aircraft
- 3.3 Ground based surveillance

4. Inspections
- 4.1 Sampling and identification
- 4.2 Observation
- 4.3 Auditing

II. On-Site Measures

1. International arrangements

2. Inspections
- 2.1 Interviewing
- 2.2 Visual inspection (including observations and surveillance by aircraft)
- 2.3 Identification of key equipment
- 2.4 Auditing
- 2.5 Sampling and identification
- 2.6 Medical examination

3. Continuous monitoring
- 3.1 By instruments (including ground based surveillance)
- 3.2 By personnel

The Royal Society Group endorses the plan inherent in Table 1 that verification should not rely on any one measure but be multicomponent in nature. This paper concentrates on the scientific aspects of inspections but some remarks on other important points in Table I that affect these aspects are appropriate here.

The central issue of detecting work on BW is the identification of specific biological agents in circumstances that cannot be justified for legitimate permitted purposes such as the peaceful use of the microorganisms or toxins in the microbiological repertoire of research and diagnostic laboratories and vaccine production units. The first requirement is to identify the high risk areas for inspection namely laboratories of high containment, facilities for national defence programmes and fermentation and vaccine production plants.

The first two aspects of the 'off-site measures' identified by VEREX (Table 1), information monitoring and 'declarations' are designed to identify these high risk areas. Much emphasis is put on 'declarations' (2 in Table 1) which, hardly surprisingly, duplicate much of the information that is sought in the replies to CBMs especially A, B, C, F and G (see Chapter 5) as the CBMs were intended to he focused on the activities that present a risk to the Convention. It may be that in the special conference following the VEREX process, the existing CBMs will be subsumed by mandatory 'declarations'. However, this is not yet certain. For the moment, the best way forward is to improve the number and quality of responses to the CBMs by the measures described in the previous chapter with the ultimate aim of making the responses mandatory. Perhaps, the most important step that could be taken immediately to provide a basis for effective verification measures is the establishment of an administrative office to chase in, document and analyse the replies to the CBMs as set down in Chapter 5. After responses to CBMs, surveillance of the literature may be the most rewarding of the five proposed methods for information monitoring. Although vital parts of a BW programme will not be published, such surveillance could indicate where relevant biological work might proceed and identify centres with the necessary expertise. Also information on technology transfer, derived through exchange of senior staff and training of students, could indicate the establishments where such work occurs. Again, an international office could monitor both these aspects (see Chapter 5).

Turning to the 'on-site measures' (Table 1), inspections inside high risk areas are the kernel of verification. Not only can they identify specific biological agents (see later, section 4) but also provide indications of whether they are being used in circumstances that cannot be justified for legitimate purposes permitted under the Convention. The facilities, equipment and records (auditing) of establishments and information received from interviewing staff should be judged in relation to the stated purpose of the establishment. As regards facilities and equipment, the items having implications in research and development (R&D) establishments are: rooms and equipment with filtered exhausts, air locks and decontamination areas, gloved safety cabinets, apparatus for aerosol experiments, effluent sterilization and facilities for dealing with infected animals. For potential production plants, these items are important and fermenters fitted with safety devices including filters on their exhausts; also harvesting equipment such as centrifuges, and freeze driers, again suitably contained, may be seen. Turning to records, lists of microbes, toxins and vaccines, research programmes, internal memoranda and reports, movements of key personnel, safety procedures, immunisation schedules, educational and training programmes, medical records and staff records are the items to look for in R&D establishments; and for potential production plants, seed and media stocks, purchases of consumables and equipment (especially filters), fermenter capacities, production figures and operational programmes should be added. Staff should be questioned regarding their work, publications, visits to other establishments and health. The above remarks apply to inspections in developed countries. In developing countries, the facilities, the equipment, the records and staff training may not be at this sophisticated level and air filtration and other safety measures may be non-existent or very primitive.

In trying to judge intent to use BW from the data obtained from the diverse enquiries set down in Table 1, some of the methods used in operational research for such complex situations might be helpful, for example, data envelope analysis (20). This analysis allows meaningful conclusions to be drawn from different types of data some of which may be incomplete and not quantitative, as might occur from the measures outlined in Table 1.

2. THE SCIENTIFIC PROBLEMS

The goal is ability to detect unequivocally infringements of Article I of the BW Convention at reasonable cost. The difficulties of achieving this goal arise from three main causes. First, the number of potential BW agents is large and is growing due to advances in microbiology, biotechnology and genetic manipulation. Second, the sciences and facilities employed for the development and production of BW agents are being used increasingly for legitimate purposes to advance the well-being of mankind. Third, only relatively small amounts of live agents are needed to cause considerable trouble which could make them particularly attractive to terrorists.

In considering methods for detecting interest in BW, it must be admitted that, no matter what technical advances are made, it will remain virtually impossible to detect by scientific means one-off, small-scale production of an agent by terrorists e.g. in a university laboratory. Good intelligence is the main counter to this threat, although tests devised to detect larger scale activities (see below) could be used on any samples gained through intelligence channels.

The target of verification measures for the present BW Convention (which does not yet cover terrorist activity - see p8), is to reveal national interest in BW. Such effort would probably be of sufficient scale to give opportunities for detection. In any national programme, there would be three progressive stages, R&D, production and weaponisation. Verification measures should focus on detection of R&D because this is where a nation newly entering the field will begin. However, attention should also be given to potential production plants especially for those nations known to have an R&D programme. If R&D and production are detected, verification could move on to weaponisation. The fact that some nations might acquire ready made BW must also be kept in mind.

There are three main scientific problems. They are outlined below with general approaches to their solution. Details of methodology are discussed later.

2.1 Remote detection of facilities with potential for work on BW

As stressed above, knowledge of the location of high risk areas is the basis for effective verification. The best, easiest and most cost effective methods of revealing these areas are good intelligence and increasing the number and quality of responses to CBMs. Other methods of information monitoring such as surveillance of the literature, technology transfer and exchange visits can help. However, in view of the poor record of responses to CBMs (Chapter 5) which may also occur for the ‘declarations’ envisaged by VEREX, the scientific question must he asked, can anything be done in the absence of information from these sources? Satellite, aircraft or ground based (within 1km) surveillance might detect physical features (security fences, well separated small buildings, effluent treatment plants) which indicate biological work. Also such work might be detected by remote interrogation of their gaseous and aerosol exhausts and/or their fluid effluents.

2.2 Unequivocal detection of BW agents during on-site and near-site inspections

An essential requirement of verification measures, is an ability to detect unequivocally one or more specific biological agents. If an agent is detected, it will spur efforts to ensure that the facilities are being used totally for legitimate peaceful purposes. Unequivocal detection of BW agents is vital for fulfilling criteria 2 and 3 for the work of VEREX (see p23) and will be needed if any disputes arise between States on alleged contraventions of the BW Convention.

All biological agents, including new ones that could be produced by genetic manipulation, can be identified by classical microbiological methods which have now been supplemented by modern immunological techniques and those of molecular biology. The latter techniques of identification can, however, take a long time and require a comprehensive spectrum of appropriate probes to be available. Also, suitably expert laboratories must be available and samples transported to them from the inspection sites. Coverage of all possible agents in this way is not feasible, certainly not at reasonable cost. The only way forward, at present, is to select relatively few agents, the identification of which, will indicate a possible *intent to use BW* in the establishment under scrutiny. Development of multiplex testing in the future could extend the range of testable agents. Now the risk of not being able to detect all potential BW agents must be accepted for a verification scheme to be realistic in relation to effort and cost.

The best choices as targets for verification are the `classical agents' i.e. those weaponised in the past. First, they will almost certainly be included in the R&D programmes of a State entering into the field for the first time, because they are more likely to have military utility and be successful than new agents and working on them will build up experience and expertise in the use of BW. Second, even if some effort is being devoted to developing new agents, one or more 'classical agents' will almost certainly be present in the R&D and production programmes of States with an established interest in BW. It is recommended, therefore, that verification measures are based on the following short list of agents.

Bacteria	*Bacillus anthracis, Yersinia (Pasteurella) pestis, Francisella tularensis, Brucella spp, Vibrio cholerae*
Rickettsia	Coxiella burnetti (Q fever)
Viruses	Venezuelan equine encephalitis virus (VEE), Tick-borne (Russian Spring-Summer) encephalitis virus (TBE)
Toxin	Botulinum toxins (sero groups A to G), Staphylococcus enterotoxin B, Ricin.

The scientific requirement is to identify these agents unequivocally by methods that are sufficiently sensitive to be used for samples from on-site inspections and, if possible, those coming from near-site surveillance of air, effluents and fermenter and other exhausts. The possible presence of microorganisms of potential BW significance in the latter will depend on the degree of containment of the facility which may not be 100% efficient for 24 hours a day especially in less developed countries. The samples from near-site surveillance will be less concentrated in the microorganisms and toxins of concern and contain more naturally occurring background biological material than those from on-site surveillance. If identification of BW agents in such near-site samples could be accomplished, it would be a big step forward. It would allow meaningful near-site surveillance during any delay between notification and accomplishment of on-site inspections. Such a delay may have to be accepted in the verification measures for the BW Convention as it has for the CW Convention. Good near-site identification methods might also circumvent some of the difficulties arising from national security considerations and commercial confidence that could restrict on-site inspections.

It cannot be over emphasised that the methods for identification of agents on the shortlist should be selected to produce unequivocal results. If a nation is accused of an interest in BW on evidence including the result of such tests, a dispute may arise as to the validity of the methods used. At least two different tests, preferably using different technology but not necessarily so, should be available. The methods must be developed by experts (probably scientists employed in defence agencies) and have been validated before use by experts in other laboratories. Field trials in appropriate R&D establishments and production plants would be necessary. International acceptance of the results of the tests is paramount. Also, the possibilities for 'jamming' the methods will have to be investigated and solutions tested. This will entail obtaining international agreement on maintaining some security on the nature of the reagents e.g. the sequences of primers for the PCR (see later). The large amount of work required to ensure complete reliability of tests on one agent underlines the importance of the recommendation that verification measures should be based on identifying a relatively small number of agents.

In addition to being unequivocal and sensitive, the methods should be capable of use at the site of inspection. Although there will be instances when samples must be taken and transported to base laboratories for further examination, the aim should be to reduce the need for this procedure as much as possible thereby making inspections both simpler and cheaper. The taking of such samples, especially of live organisms, for later identification by conventional microbiological procedures is fraught with difficulty. First, there are the technical aspects of collecting the sample by methods which preserve viability and of suitable transport media, temperature and packaging. Then, the taking of samples, the transportation, the laboratory examination and the provision of the report must be unambiguous. Triplicate samples would be needed from every sampling point, one for the inspected, one for the inspection and one held in reserve for analysis by a third party. The taking of samples, their labelling and provision of receipts would have to be documented and witnessed. There are also the formal requirements for transporting samples from one country to another. Finally, commercial confidence may be broken by the taking of samples. It is hoped that these complicated procedures could be restricted to when positive indications of BW activities were found and/or when disputes arise between inspectors and inspected. This will happen only rarely. For the great majority of cases, *provided the identification methods are reliable and agreed,* on-site analysis in the presence of the inspected should provide sufficient evidence to suggest that the Convention is not being contravened. On-site testing would be simpler and cheaper than taking samples for off-site testing; any complication could be sorted out before the inspectors left the site.

To be used on-site, the methods should take only a few hours to complete, require only portable equipment and be maintainable without sophisticated laboratory facilities. It will be tempting to adopt for verification detection, methods that are designed for protection of military personnel on the battlefield. An important difference between the two requirements must therefore be emphasised. For the battlefield, ultra rapidity is needed to trigger immediate protective measures. For verification purposes, rapidity is not the paramount requirement. Sensitivity, specificity and complete reliability for the shortlist of agents are far more important. To ensure these requirements, a reasonable increase in the length of the test can be accepted.

Finally, the importance of knowing what microorganisms and biological products are being (or should be) used or produced for peaceful purposes within an inspected facility, should be emphasized. This knowledge should be obtained through replies to CBMs. If also

the details of the tests used to detect these microbes and/or products, were available at the inspected facility it would help in distinguishing between legitimate use and work on BW agents.

2.3 Detection of agent development and delivery systems

If potential BW agents are identified in a R&D establishment or their production and use for peaceful purposes are admitted in replies to CBMs, the possibility of their development as offensive BW must be investigated.

Already in the introduction to this chapter we have noted that a thorough on-site inspection of the facilities, equipment and records of the establishment and talking to staff can indicate suspicious activity when the information gained is judged against the stated purpose of the establishment. Evidence for relatively large-scale production of virulent agents under contained conditions should be sought remembering that the scale of operations would be less for live microorganisms (which are effective in small quantities) than for toxins, and in developing countries, the degree of containment, if any, may be low. The possibility of work on BW occurring side by side with legitimate operations should be kept in mind.

The clearest indication of intent to use BW would be the detection of delivery systems that might or might not contain agents. Munitions (shells, bombs, missile warheads) containing devices for spreading dried agents such as a screw discharge system would indicate intent. Also devices that could be used on aircraft for spraying liquid suspensions of agents would be suspicious if not clearly seen to be for legitimate agricultural use. Facilities for, or records of, large scale aerosol experiments in chambers or in the open air would also be significant.

Turning to scientific problems in this area, an ability to interrogate the contents of closed bulk containers or munitions for BW agents might be needed. While it is accepted that rapidly cultivated, short lived vegetative microorganisms such as plague bacilli might be produced for immediate use, stockpiling of other biological agents could be necessary. Toxins such as botulinum toxin would, like CW, have to be produced in relatively large quantities and stored in containers or munitions before use. Also, anthrax spores are perhaps the most favoured BW because they can be stored for long periods in liquid suspension, or dried, as well as withstanding aerosolisation. Purchased BW would certainly be in bulk containers or munitions.

Another scientific problem is to be able to distinguish virulent strains of potential BW agents which could be used offensively from less virulent strains that are used for vaccine production.

Finally methods of distinguishing munitions designed for spreading BW from conventional high explosive or CW munitions would be helpful.

3. METHODS FOR REMOTE (SATELLITE, AIRCRAFT) AND NEAR-SITE (WITHIN 1 KM) DETECTION OF WORK ON BIOLOGICAL MATERIALS

This section is concerned with the identification of R&D establishments and production plants that deal with biological materials (i.e. high risk areas). Although some indication of BW activity may emerge, the methods are essentially non-specific, detecting peaceful and possible prohibited activity alike. Specific identification of agents by near-site and on-site inspection is the subject of the next section.

It is accepted that remote and near-site sensing of potential high risk areas is second best to provision of hard data from intelligence sources or accurate replies to CBMs/'declarations'. Such sensing is likely to be complex, costly and less reliable. Nevertheless the scientific possibilities should be explored because the required information may not become available from the other sources. Indeed, VEREX has listed remote sensing and off-site inspections as measures to be considered and evaluated in establishing verification procedures (Table 1).

3.1 Possible targets for detection methods

The following items apply particularly to identifying potential production plants where gaseous, aerosol and effluent discharge will be greater than from R&D establishments. Nevertheless, some escape from the latter will occur and could form the basis for detection although more difficult. The size of facilities for producing live biological agents may be smaller than those for toxins and be based on glassware culture rather than fermenter techniques. Despite this, some gaseous, aerosol and effluent discharge will occur especially if containment discipline is slack.

3.1.1 Visual features. A combination of security fences, separated buildings, mechanical ventilation, filters fitted to air exhausts, effluent disposal units, animals and/or animal houses might suggest biological R&D. In addition to these items, production plants might have large fermenter exhausts although these are easily concealed. Also, fermentation plants use a lot of water so evidence of large water inputs and fluid effluents may be indicative. In the tropics, fermentation plants need substantial cooling equipment.

3.1.2 Production of heat. Temperature profiles over biological plants, although higher than the surrounding environment, are much cooler than similar profiles over major industrial (e.g. steel) plants and chemical production factories. So-called 'low grade heat' is typical of a biological plant but it is not a complete discriminator in this respect because other light industrial activities have similar characteristics.

3.1.3 Materials in fermenter and ventilation exhausts to the atmosphere. When air is used as an oxygen supply for fermenters, the oxygen concentration changes only slightly from about 21 to 18% v/v and hence it is not a likely basis for detection. CO_2 is the main gaseous product of microbial growth. Fermenter exhausts contain about 1-2% v/v compared with about 0.04% in the air. Measurement of CO_2 concentration in fermenter exhausts may, therefore, indicate biological activity. Also, biological processes including microbial activity can change the ratios of ^{12}C to ^{13}C in its products including CO_2 (21). It is conceivable that a comparison of these ratios for CO_2 in fermenter exhausts with those of outside air may indicate biological activity. However, most of the CO_2 in the atmosphere is of recent biological origin (respiration by animals, plants and soil microorganisms). Also,

fossil fuel burnt in power stations is to some extent ^{12}C enriched already. Nevertheless, the approach is worth investigating. Other gases (H_2, oxides of N, CH_4 and H_2S) can be present depending on the nature of the fermentation. Little information is available on the amounts in exhausts.

Proteins, carbohydrates, nucleic acids and lipids (free or in intact microbes) are present as aerosols in unfiltered fermenter exhausts. The amounts are determined by the nature of the culture, the rate of aeration and other factors; dry weights of 8-250mg/m^3 and microorganism contents of 10^4-10^5/m^3 have been recorded (22). Such aerosols can be removed by cyclone collectors and HEPA filters on the exhausts. They would definitely be fitted in advanced countries if pathogens were being grown but not necessarily so for non-pathogenic cultures. In less developed countries, the frequency of fitting filters would probably be less. Although in reduced amount, unfiltered exhausts from R&D laboratories and production units using glassware culture will probably contain similar materials. Whether or not the aerosols of fermenter and other exhausts can form the basis for detection will depend on the degree of containment achieved. Only in the most well run facilities will this be 100% efficient for 24 hours a day.

Medium constituents (glucose, amino acids, phosphates) will also be present in aerosols of fermenter exhausts.

Finally, most fermentation plants especially those dealing with prokaryotes have an odour. Like pheromones (23), the minute amounts of airborne compounds responsible may form a basis for near-site detection of biological work. Some odours are dependent on the substrates used for fermentation e.g. H_2S from SH groups on amino acids and other compounds, methylamine from choline, skatole from tryptophan and corn steep liquor used for penicillin production. If such substrates are needed for growth of particular organisms, e.g. SH containing compounds for anaerobes, the odours may provide some indication of the microorganism being grown.

3.1.4 Materials present in effluents, sewage and soil washings. All the materials mentioned in the previous section, apart from the gases, could be present in fluid effluents from production plants and R&D establishments. They could therefore indicate biological work. If a fermentation plant is producing an extracellular toxin, the bacterial source of the toxin, which may be substantial in amount, will have to be discarded. It, or any other organisms that grow on biomass, may be detected in effluents or disposal dumps. The chemical and biological profile of the waste may not only indicate the overall biological activity (e.g. the presence of bleach would suggest work on pathogens) but even the nature of the fermented organism. Such profiles could be investigated for important sources of BW agents e.g. *Clostridium botulinum,* and also for organisms such as *E. coli* which could be the vehicles for the production of genetically engineered toxins.

3.2 Potential methods of detection

3.2.1 Visual and heat imagery by satellite and aircraft. Significant features of the facility (see above) can be seen. The relatively low heat image of biological production plants is a most significant feature and infra-red imagery may be able to detect it but it must be remembered that other light industrial activity can produce similar images.

3.2.2 Spectroscopic interrogation of fermenter and room exhausts. There is potential in this approach for near-site (within 1 km) surveillance from the ground or, if allowed, low flying aircraft. Remote surveillance by satellite or high flying aircraft is not promising because of the increased distance and the possibility of atmospheric interference.

Gases and possibly other small molecules in aerosols (e.g. medium constituents) may be detected by laser DIAL systems (differential absorption LIDAR i.e. light detection and ranging) using optical and infra-red frequencies. Two laser beams of different wavelength would be directed at the exhaust and specific materials present would be indicated by detecting differential absorption of the beams in the reflected light. DIAL systems work best when they are directed upwards from the ground; if used in a downwards direction, ground based materials can interfere. They (and ordinary single laser LIDAR) have been used to track smoke plumes from power stations. Rain and water vapour interfere. Portable (suitcase size) infra-red spectrometers are available. Laser DIAL can be made specific for certain molecules: used at infra-red frequencies it should he able to detect the higher concentration of CO_2 in fermenter exhausts compared with that in the normal atmosphere. Detection of a profile of gases may differentiate fermenter exhausts from those of boilers and other heating plants.

Measurement of $^{12}C/^{13}C$ ratios is possible for small molecules like CO_2 by microwave spectrometry. Whether it is sensitive enough to detect any differences in this ratio between the CO_2 in fermenter exhausts and that in the outer atmosphere (see above) could be investigated. For example, the $^{12}C/^{13}C$ ratios for exhausts of known biological plants (e.g. a brewery) could be compared with those of the outside air and also of other CO_2 producing plants (e.g. oil and coal burning power stations).

Larger biological molecules in aerosols, such as proteins, porphyrins and other biological materials, can be detected by laser LIDAR at relatively short wavelengths (300-600 nm). It should be investigated for near-site surveillance since its range is about 1km. However, natural biological contamination in the air will interfere and its effect must be gauged by preliminary experiments. Laser LIDAR at these wavelengths could not be used for remote surveillance.

3.2.3 Detection of biological materials in air samples, effluents, sewage and soil washings by electrochemical, enzymic and other means. Air could be sampled around the facility (100 1/min) by ground based cyclone collectors. Less likely, but possible, samples from fermenter and other exhausts might be taken by similar collectors in low flying aircraft. The sample is collected in a liquid medium. Also, gases and other materials present in liberated aerosols could be collected by leaving *absorption tubes* (tubes containing appropriate absorbents) around in the vicinity of the establishment for several days. The sample would have to be desorbed before analysis. Effluent, sewage and soil samples from near the establishment should be easily available. The following methods apply to all these samples but some samples, e.g. those of soil and sewage, will be far more contaminated with extraneous biological materials than others, e.g. samples from fermenter exhausts and effluents.

Electrochemical and enzyme based sensors using various transducing devices have been used to monitor media constituents (glucose, amino acids) and other biological materials in fermentation processes. Electrochemical and other sensors have been used in submarines for measuring gases (e.g. H_2S and CO_2). These sensors are stable and relatively small. There is no reason why they should not be sufficiently portable for detection of general indicators of biological activity during near-site surveillance. Sensitivities can reach nanogram (ng)/ml of sample. Also, dipstick-type enzymic, immunological and biochemical methods are becoming available for identifying serum and urine constituents in medical diagnosis (e.g. glucose in diabetes and hormone changes in pregnancy). Such tests would be convenient for detection of glucose, amino acids and other indicators of biological activity in effluents from fermenters and other fluid samples.

Turning to detection of bacteria and their products in the air and effluents, chemiluminescence and bioluminescence methodology is well established for water and airborne bacteria. Haem, liberated from bacteria by NaOH, can either react with luminol directly to produce chemiluminescence, or can catalyse the reaction between luminol and an oxidising substrate (e.g. perborate) to produce bioluminescence. In both cases, the emitted light can be measured and is proportional to the amount of haem released. These methods can detect the haem from about 10' bacteria/ml but since most biological materials contain haem, they are very prone to interference by environmental contamination.

The potential of using for identification purposes the airborne compounds responsible for the odour of fermentation plants should be stressed. First inspectors could be made familiar with the odours of typical fermentation plants. Then, if these compounds could be identified, it might lead to the design of multiple sensors that would react, either to air passing over them or to the presence of the compounds collected by cyclone collectors or absorption tubes. There is a burgeoning interest in using integrated microelectronic arrays of solid-state gas and odourant sensors ('electronic noses') for discriminating between various alcoholic and other beverages, tobacco blends and coffees; effort in the UK is concentrated in the Universities of Manchester, Warwick and Southampton (24,25). Discussions on the potential of this method may be fruitful.

Finally, remote detection of biological materials in effluents by spectrometers mounted in aircraft is not out of the question. Laser fluorescence spectrometry has been used by the US Coast Guard Service for detection of oil slicks on seawater.

In summary, if the locations of high risk areas are not available from intelligence sources, replies to CBMs and other methods of information monitoring, the following methods have potential for identifying facilities capable of biological work on BW.

1. Remote (aircraft, satellite) visual and infra-red imagery to reveal facilities needing closer attention.
2. Near-site (within 1km) spectroscopic interrogation of gaseous and aerosol exhausts.
3. Biochemical testing of air and effluent samples: although primarily directed to detecting non-specific indicators of biological activity some clues as to the nature of the fermented microorganisms may be gained.

These methods would be difficult and costly to mount and maintain for routine use. This underlines the importance of the measures advocated in Chapter 5 for trying to improve the number and quality of responses to CBMs.

4. METHODS FOR ON-AND NEAR-SITE (WITHIN 1 KM) IDENTIFICATION OF SPECIFIC BW AGENTS

4.1 Principle

The methodology should be based on identifying only the chosen shortlist of BW agents and use of at least two internationally validated methods for each agent (see above). As far as national security and commercial confidence will allow, the microorganisms and products being worked on for legitimate purposes and the details of the tests used to detect them should be ascertained before the inspection so that clear distinctions can be drawn.

4.2 Levels of sensitivity

Under optimal conditions, the methods described below should be capable of identifying 10 to 10^4 bacteria or virus particles or genomes, and 1 picogram (pg) to 1 ng of toxin in 1 ml of sample. Even greater sensitivities might be obtained, e.g. in the diagnosis of HIV infection there are aims to detect one viral genome in 1 ml of blood. The methods are however critically dependent on the degree of background contamination. If this is relatively small e.g. in swabs and culture samples taken during on-site inspections, there should be no difficulty in reaching the lower end of these ranges. Samples taken during near-site inspection will be less concentrated and more contaminated than those taken on-site although some, e.g. air samples and those from fermenter exhausts and effluents, will be cleaner than others e.g. samples of soil and sewage. To achieve the lower end of the sensitivity ranges for these samples (which is desirable because of the importance of near-site surveillance in any delay of on-site inspections; see above), concentration and removal of contaminants will be needed e.g. by the use of specific immunosorbents. Also additional methods for countering the adverse effect of gross environmental contamination on the detection and identification of relatively few microorganisms, may arise from the PROSAMO (Planned Release of Selected and Modified Organisms) project. This project is funded by the DTI, BBSRC and some industrial companies to study the problems, including detection, of the release of genetically modified organisms into natural environments such as soil (26).

4.3.Source of samples

4.3.1 On-site. Frozen or dried culture collections; currently used cultures; container and fermenter contents; swabs from benches, apparatus and filters on rooms, safety cabinets and fermenters (filters should be sampled on the inlet side); effluents before treatment, sewage and specimens from infected animals. Air samples could also be taken.

Monitoring serum for antibodies to BW agents is a powerful method of verification. Hence, every endeavour should be used to obtain samples from personnel by taking blood at the time of inspection, together with stored samples that may have been taken from personnel when joining the establishment. It is realised that the taking of blood samples may not be allowed in some countries without the consent of the person concerned. The taking of saliva or sweat samples, both of which contain antibodies, may be more acceptable.

4.3.2 Near-site. Near-site sampling is a large operation and should only be undertaken if on-site sampling is restricted. Air sampling could provide important information and should certainly be conducted at ground level. If possible politically, and suitable aircraft are available, samples from fermenter exhausts could be taken. Airborne agents may be picked up by leaving tubes containing specific immunosorbents in the vicinity of the establishment for a few days. At least 10 litres of effluents should be collected. Soil and sewage samples should be taken. Again, collection of blood (for sera) from people and animals in the vicinity should be undertaken if politically possible.

4.4 Collection and treatment of samples

The sample should be as concentrated as possible in a small volume of liquid. Viability is not important for samples required for the on-site methods of identification. In the small number of cases when a sample must be transported for further examination at a base

laboratory (see p28), the method of taking the sample and the liquid into which it is collected, should preserve viability if the identification methods demand it. Also, suitable transport media for the agents on the shortlist will have to be selected.

For on-site identification methods, except those for extracellular toxins, the samples will have to be treated with a lytic or disruptive material (e.g. a detergent) to liberate specific antigens and nucleic acids. Any material added for this purpose must not interfere with subsequent test procedures. Different lytic materials may be needed for different agents on the shortlist. Samples from the various sources would be treated as follows:

4.4.1 Culture collections, current cultures, container and fermenter contents. Use directly for tests by adding the lytic material.

4.4.2 Swabs. Elute and treat with a solution of the lytic material.

4.4.3 Air. Near-site air will be collected in a cyclone collector with the lytic material being either present in the liquid or added later. Except perhaps for air being collected in a fly-past, there is no need for the extremely fast sampling (1000 1/min) required for battlefield identification. A cyclone collector giving 50% efficiency at 100 1/min is adequate as long as it is used for a sufficient period for a suitably large volume to be sampled. Absorbents that may have collected aerosol material (see above) must be treated with a suitable desorbent. If specific immunosorbents were used, the contents of absorption tubes might be used directly for an identification test (see below).

4.4.4 Effluents and sewage. These materials will have to be concentrated because of their low contents of agents. Also, any background contamination should be reduced. This can be done by membrane filtration but use of agent-specific immunosorbents would be the best method. Samples would be suspended in a solution of the lytic fluid.

4.4.5 Soil samples. These should be washed and the washing treated as effluents.

4.4.6 Blood samples. Sera should be prepared immediately and preservative added.

4.5 Methods of identification: physico-chemical

There are many physico-chemical methods for detecting microorganisms but most are non-specific. Mass spectrometry (MS), laser immunofluorescent spectroscopy and laser Raman spectroscopy show the most promise for identification of specific microorganisms.

4.5.1 Mass spectrometry. This is already used and shows much promise for the future. In pyrolysis MS, the sample is heated in a non-oxidising atmosphere and the small fragments are subjected to MS. Pyrolysis by laser beam is very efficient, producing fast heating and capable of use with less than ng quantities. In the laser microprobe analyser, aerosol samples are collected on impactors or filters, particles (e.g. bacteria) are located by microscopy and individually pyrolysed by a frequency quadruplet neodymium-YAG laser which can focus to one micron. In other systems, the particle beams produced by passing aerosols through fine nozzles go directly into the MS chamber where they are pyrolysed by various types of lasers. Fast atom bombardment MS, in which the sample is bombarded by

positive and negative ions, detects larger molecules than ordinary MS. Conducted directly on lysed bacteria it looks promising for identification of pure cultures. Secondary ion MS in which a surface under bombardment with primary particles from the specimen emits secondary particles capable of MS analysis, can analyse pg quantities of material.

4.5.2 Laser immunofluorescence. Whole microbes or lysates are treated with specific antibody coupled to a fluorosphere dye. A laser beam is directed at the sample and the emitted fluorescence is measured in a spectrophotometer.

4.5.3 Laser Raman spectroscopy. The sample is subjected to laser monochromatic light (UV for biological materials) and scattered light of longer and shorter wavelengths is measured. It has been used on single particles (laser, micro, Raman spectroscopy) and bulk samples.

Although these methods show promise for laboratory identification of small quantities of microorganisms (even individual bacteria), they appear not relevant to on-site testing at present. The equipment is sophisticated and mostly not portable. However, the position may change for MS. Already, apparatus for pyrolysis MS transported in a small lorry is being investigated for battlefield detection of agents. Also, ion-trap mass spectrometers of suitcase size (75 kg) are being used for on-site soil and water analysis for specific chemicals.

4.6 Methods of identification: biological

Two methods, amplified reaction with antibodies and the polymerase chain reaction (PCR) (27) should reach the levels of detection required. Reactions with cell receptor preparations has been suggested as another rapid method of detection of microbes and toxins (27). At present however, such preparations are too fragile, short lived and uncharacterized for the method to compete with the two well-established procedures.

4.6.1 Reaction with antibodies. This method can be used for toxins as well as bacteria and viruses. Polyclonal and monoclonal antibodies raised against the agents on the shortlist would be needed. Polyclonal antibodies may be better than monoclonals for detecting different strains of a particular agent.

Enzyme linkage is the most used method for amplification of antibody reaction. In the enzyme-linked immunosorbent assay (ELISA) procedure, antibody and antigen react together and then the enzyme produces a measurable colour on addition of an appropriate substrate. Further refinements, like the avidin-biotin peroxidase indicator system can increase sensitivity. Indication from other fields suggest that 10^4 virus particles or bacteria and 1 ng toxin can be identified by laboratory based ELISA tests which can be completed in 2-3 hours. Also, because extreme rapidity is not needed, enzyme-cycling may increase the amplification of ELISA type methods sufficiently to attain sensitivities of 10 virus particles or bacteria and 1 pg toxin. Furthermore, advances in chemical engineering may raise the avidities and specificities of antibodies and enzymes thereby increasing sensitivities.

There are other methods of amplifying antibody reactions e.g. by coupling antibodies to fluorescent dyes and detecting their reactions with antigens by optical methods. At present, fluorescence procedures on eukaryotic cells will detect 500 molecules per cell.

The ELISA tests described above can be used equally well for detection of antibodies to BW agents in the sera of personnel and animals present on-site and/or in the surrounding area. The agent on the shortlist would be the reagents for the tests. The presence of

antibody in the sera will depend on the exposure dose and the antigenicity of the particular agent. Indications from other fields suggest that the ELISA tests could detect ng quantities of such antibodies.

4.6.2 The polymerase chain reaction (PCR). The essence of this reaction is hybridization of gene probes with specific nucleotide sequences in the nucleic acid of the agent. Such hybridization, amplified by enzyme linkage or fluorescent markers, can be used directly for ultra-rapid detection of agents on the battlefield. It can also be used for verification purposes in the far more sensitive PCR whereby the nucleic acid segment of the agent is multiplied several million fold by 30-40 reactions in a few hours. The requirements are the target DNA, a pair of synthetic oligonucleotide primers, deoxynucleotide triphosphates, a thermostable DNA polymerase (Taq polymerase) and limited laboratory facilities. Experience in other fields suggest that 10 or less virus particles or bacteria can be detected in 1 ml of a sample. The PCR will not identify toxins *per se* but it might do so indirectly by virtue of any nucleic acid that contaminates the toxin. PCR can work on samples that have been inactivated by drying, heat or formalin, a great advantage for use in on-site identification. It may well detect the remains of agents in effluents, in samples taken after decontamination of laboratories and possibly in aerosol samples collected from fermenter exhausts. Appropriate nucleotide sequences of the genomes of agents on the shortlist must be chosen so that primers can be prepared. Primers with less than optimal specificity may have advantages for detecting different strains of particular agents. Work in other fields has shown that appropriate primers of more than one microorganism can be included in the same PCR reaction. This time-saving procedure might be used for identification of different BW agents of the shortlist in the same reaction. Dot blotting with a labelled DNA probe can be used as the final check on the identity of the agent (this has already been demonstrated by the amplification process occurring with the specific primers).

PCR has one snag: it is prone to interference by contamination. Hence, preliminary experiments must be done to find out whether naturally-occuring microorganisms and other biological material that might occur in the air and effluent samples (see above) could interfere with the specific identification of agents on the shortlist. Heavily contaminated samples e.g. of sewage or soil may need preliminary selective concentration e.g. by an immunosorbent. Interference with a PCR test, either accidentally through environmental contaminants or deliberately, can be detected and probably overcome by repeating the PCR with a different set of primers.

4.7 Modes of deployment of the methods

The aim is unequivocal identification of BW agents at the sensitivities required by methods that can be used at the site of inspection. Experience in other fields suggests that sensitivities down to 10 virus particles or bacteria and 1 pg of toxin can be reached (see above) provided the sample is reasonably clean and *laboratory tests can be done.* Hence, the first question on modes of deployment is what are the minimal laboratory requirements for conducting ELISA and PCR tests. The second question is whether conveniently used test systems that do not require laboratory facilities are sufficiently reliable and will they provide the required sensitivities of identification.

4.7.1 Tests using limited laboratory facilities (power and water supplies, sink and bench). The ELISA assay system could be used provided reagent plates had been coated beforehand

with appropriate capture antibody (or antigen for interrogation of sera) and the remaining reagents were in portable packs. If need be a portable spectrophotometer could be used. Also portable multiplex comb-ELISA systems are becoming available. The stabilities of reagents needed for all the agents on the shortlist would have to be checked beforehand. If immobilized antibodies were used in absorption tubes for near-site surveillance of air or in methods of concentration of effluents (see above), it might be possible to use this as the capture step of an ELISA test scheme.

PCR tests require a PCR cycling machine, a centrifuge and a filtration system in addition to reagents (see above). PCR machines are now available in suitcase size and can accomplish 30-40 reactions in under 1 hour.

4.7.2 Dipstick tests. These tests, based on antibody antigen reaction, are available for a variety of medical tests e.g. for pregnancy. Capture antibody is coupled to an absorbent pad to which the sample is applied. Subsequent treatment with enzyme-linked antibody and substrate, either by dipping the stick in reagent solutions or by a wick system within the dipstick which produces a colour. CBDE has carried out research into the adaptation of this system to detect specific BW agents. Such tests, simple, rapid (less than 1 hour) and not requiring laboratory facilities, would be most convenient for inspections. Experience in other fields suggest that it might be possible to detect 10^4 bacteria or virus particles and 1 ng of toxin but not 10 microorganisms or 1 pg toxin. If the sensitivities of these type of tests could be raised, it would be a major step forward because of their convenience e.g. for testing effluents. Enzyme-linked gene probes could also be adapted for dipstick type tests.

4.7.3 Biosensors. There is a burgeoning interest in using optical or electrical devices (transducing systems) to detect, amplify and quantify biochemical reactions rapidly and conveniently. Such devices have already been coupled to enzymes and to antigen/antibody reactions and undoubtedly will be used with gene probe hybridization. Biosensor research holds the promise of convenient and semi-automated methods of verification which do not need laboratory facilities. There are indications that the enzyme and antigen/antibody based biosensors can identify 10^4 bacteria and 1 ng of antigen but significantly higher sensitivities have not yet been achieved. Nevertheless, the fact that time can be taken in verification procedures may allow methods requiring equilibrium to be established between reactants, to work at greater sensitivities than when ultra rapidity is the aim. Many different transducing systems are being investigated. Some examples are as follows:

1. Surface enhanced Raman spectroscopy, Raman light scattering is affected by antigen antibody reactions occurring on metal surfaces; a resonance dye is attached to the reacting antibody.
2. Evanescent wave immunoassay uses a fibre optic system and fluorophore labelled antibodies. Antibody antigen reactions cause changes in the evanescent wave of internally reflected light.
3. Surface plasmon resonance. A light beam is directed on a metal film deposited on either a prism or diffraction grating; antigen antibody reactions on that metal film affect the response.
4. Light addressable potentiometric sensor. Changes in pH produced by the enzyme (urease) of an ELISA system are monitored potentiometrically and produce a photo-response by catalytic hydrolysis of an appropriate substrate.

5. Surface acoustic wave devices. Antigen antibody reactions affect the frequency of oscillations of high frequency quartz transducers.

All these transducing systems can be coupled to direct hybridization by gene probes and to the final stage of PCR. Also multiplex PCR systems where arrays of oligonucleotide detectors are coupled to electronic microchip systems are now being designed.

None of these biosensors has yet a proven record of reliability for identifying agents at high levels of sensitivity. Expert opinion is needed on which systems show most promise and are capable of being sufficiently portable for verification purposes at sites that lack laboratory facilities. Then, a substantial research programme is needed to identify the chosen shortlist of agents in the presence of possible interference by unknown materials in the environment.

4.7.4 Continuous monitoring. This would not be cost effective. If staff were involved it would be expensive. Automatic biosensors would need regular maintenance and be easy to circumvent.

4.8 Recommended procedure for the immediate future (5-10 years)

Dipstick and biosensor technologies are still in the development stage and cannot yet be guaranteed to provide reliable, unequivocal identification of all the agents on the shortlist at high levels of sensitivity. In contrast, laboratory use of ELISA and PCR could probably achieve this goal easily and quickly. The main need is appropriate antibodies and primers. The laboratory requirements are minimal; reagents, plastic ware, a spectrophotometer, a PCR cycling machine, a centrifuge and possibly a filtration pump; and all are portable. They could be used with facilities normally found in a kitchen (power and water supplies, a bench and a sink) which are likely to be available at any location of inspection. Particular precautions to protect against contamination of samples during the PCR procedure would have to be taken. The simplest, cheapest and most effective method of reaching the goal of verification measures quickly, may be to train inspectors to use portable equipment in this way. The use of dipsticks and multiplex biosensors could follow if and when they prove effective.

5. METHODS FOR DETECTING AGENT DEVELOPMENT AND DELIVERY SYSTEMS

Three scientific problems have been mentioned (p29), detection of large quantities of BW agents in closed containers, identifying virulent strains of the agents that might be used offensively and methods of distinguishing munitions designed for use with BW.

5.1 Detection of large quantities of BW in closed containers

The closed containers may be in production facilities or found as munitions (tanks for spraying, shells, bombs and missiles). The containers are likely to be made of steel or ferrous metals and the agents will be present in water suspension or dried.

Four methods of interrogation were considered: X-ray, NMR, sonar and neutron activation analysis. X-rays cannot 'see' microorganisms or toxins. Microorganisms might be detected by NMR scanning but the apparatus is vast, and metal containers would interfere with the magnets. Sonar would show if the containers were full or empty with liquids or

solids but it would not detect microorganisms or toxins. Only neutron activation analysis (NAA) shows promise for detecting biological materials though not specific agents.

5.1.1 Neutron activation analysis (NAA). This method identifies elements from the wavelengths of gamma rays released by neutron bombardment. It detects C, H, 0, N, S, C1, Si and A1 in coal and oil-bearing substrates (28,29). Currently, it is being developed to detect explosives in closed containers. In oil well logging, neutrons penetrate 6-12 feet in high hydrogen environments which absorb strongly. Steel and ferrous metals absorb less strongly and penetration is better. Sensitivities are reasonably high provided the material is interrogated for a few hours. When less time is available e.g. for detection of explosives in luggage at airports, the method is less sensitive (e.g. 10g of a typical N-containing explosive). Measurements have a variation of +/- 25%.

There are two potential portable sources of neutrons. Chemical sources (^{241}Am/Be or ^{252}Cf; they have different neutron characteristics and can be used for different purposes) are small and together with a separate gamma ray monitor are suitcase size. The other source is a fast neutron accelerator which needs a power supply. Together with a gamma ray detector, a cooling system and shields it is transportable (4-5 feet square) rather than portable, but future developments in relation to detection of explosives may provide smaller equipment. The radiation hazard of using neutron sources is less for the fast neutron accelerators since neutrons are produced only when power is switched on whereas chemical sources emit rays constantly.

BW consist of bacteria, viruses (including the debris of animal cells which must be used to grow viruses and will probably be left in the suspension) and toxins (mostly proteins or peptides). The main elements present are C, H, 0 and N with P, S, CI, Na, K, Ca and Mg at much lower levels (30). Proteins contain about 53% C, 7% H, 17% N, 23% O and 1% S. Dried bacteria contain about 49% C, 7% H, 21% 0,14% N, 2% P and 0.5% S (31). If the BW agent is in the form of a water suspension H and 0 will be in much greater proportion even if interrogation is directed at the bottom of the containers which will contain the sedimented agent.

C, H, O, N, S and possibly P can be detected by NAA. The high proportions of C, H, O and the relatively low proportions of N and especially P and S, should distinguish biological material (possibly in aqueous suspension) from high explosives (high N, no P and S), mustard gas (high S, no P), cyanide (high N and no S and P) and nerve gases (high P, and usually no S).

In summary, NAA should be investigated for detecting biological material within closed containers. Then, if such material is detected, thorough swabbing or washing around the area of the filler caps may yield sufficient material for identification of the specific agent by the extremely sensitive PCR (see above).

5.2 Identification of virulent strains of BW agents

This is a matter for base laboratory investigations. Any isolates of potential BW agents obtained from on-site or near-site inspections of establishments that have not admitted the presence of such agents; and any strains found in laboratories that have admitted to the possession of agents but are not justified by the stated peaceful purposes should be sent to two independent base laboratories for virulence testing and comparison with other virulent strains.

5.3 Identification of munitions designed for BW

Aircraft fitted with spraying devices will be easily recognisible. However, special detonators or screw devices for the spread of powdered agents may be present in BW shells or bombs that look from the outside like conventional weapons. If the munitions cannot be dismantled, an X-ray should reveal any special design. X-ray equipment is cumbersome but transportable equipment should be available.

6. SUMMARY OF CONCLUSIONS

1. Verification of compliance to the 1972 BW Convention should not rely on any one measure but be multicomponent in nature. This chapter concentrates on the scientific aspects.

2. The central issue of detecting work on BW is the identification of specific biological agents in circumstances that cannot be justified for legitimate purposes permitted by the Convention.

3. The first requirement is to identify for on-site inspection high risk areas namely laboratories of high containment, facilities for national defence programmes and fermentation and vaccine production plants: the best and easiest method is from intelligence sources and accurate replies to CBMs A, B, C, F and G (see Chapter 5) or 'declarations' if they subsume CBMs.

4. In the absence of hard data from these sources, a combination of remote (satellite, aircraft) visual and infra-red imagery, near-site (within 1km) spectroscopic interrogation of gaseous and aerosol exhausts and biochemical testing of air and effluent samples has potential for identifying high risk areas. These methods will be time consuming and expensive.

5. An essential requirement of verification measures is an ability to detect unequivocally biological agents during on-site inspections and near-site if the latter are curtailed.

6. Identification of all possible agents including those that might be produced by genetic engineering, is not realistic in relation to effort and cost. The objective should be to reveal possible *intent to use BW* in the establishment under scrutiny by unequivocal detection of relatively few agents. At present these agents should be the 12 'classical' agents i.e. those weaponised in the past and most likely to be used by nations newly entering the field. The development of multiplex testing in the future could extend the range of agents detectable by the methods described below.

7. For each agent there should be two internationally validated identification methods capable of use at the site of inspection. Samples should be transported to base laboratories for investigation only when positive indications of BW activities are found and/or when disputes arise between inspectors and the inspected.

8. Under optimal conditions, enzyme linked immunosorbent assays (ELISA) and the polymerase chain reaction (PCR) are capable of identifying 10-10^4 bacteria or virus particles or genomes and 1pg to 1ng of toxin in 1ml of sample. These levels of sensitivity are more than adequate for samples taken on-site and near-site.

9. After comparison with dipstick and biosensor technologies, it is recommended that the simplest, cheapest and most effective method of providing unequivocal identification of all 'classical' agents at high levels of sensitivity in the immediate future (5-10 years) is *laboratory use of ELISA and PCR.* The laboratory requirements are minimal and all are portable. They could be used with facilities normally found in a kitchen (power and water supplies, a bench and a sink) which are likely to he available at any location of inspection. Inspectors could he trained to use ELISA and PCR with portable equipment.

10. If potential BW agents are identified by on-site inspections or their use is admitted in replies to CBMs, assessment on whether or not they are used in circumstances justified for legitimate, permitted purposes must be based on judging whether the facilities, the equipment, the records and information obtained by interviewing staff during on-site inspections fit with the stated purpose of the establishment under scrutiny. Signs of large scale production might indicate BW activity.

11. Special attention should be directed to detecting delivery systems such as munitions with specialized spreading devices and aircraft fitted with spraying equipment; also facilities, or records of, large-scale aerosol experiments in chambers or in the open air.

12. Scientific aids are NAA interrogation of closed containers or weapons for BW agents, base laboratory virulence testing of suspicious strains of potential BW agents and examination of weapons by X-rays for specialized detonators or spreading devices.

7. TECHNOLOGY TRANSFER

Technology transfer in relation to the development of BW is a subject of much current interest to many nations including the UK because of clear indications of proliferation of BW. It is estimated that about 10 nations are already interested in the subject although they have not been named (Appendix VII). Some of them may be developing nations which consider BW as strategic weapons in lieu of nuclear weapons.

1. INTRODUCTION

Technology transfer directly related to BW is specifically forbidden by Article III of the BW Convention (Appendix III) which reads:

> *'Each State Party to this Convention undertakes not to transfer to any recipient whatsoever, directly or indirectly and not in anyway assist, encourage or induce any State, group of States or international organization to manufacture or otherwise acquire any of the agents, toxins, weapons, equipment or means of delivery specified in Article I of the Convention.'*

Checking compliance to Article III is an immensely difficult task both at the international level of scrutiny of State parties and by the State parties themselves in relation to the activities of their citizens. The difficulty arises from the fact that the same basic knowledge of microbiology and biotechnology and similar R&D facilities and production plants are needed for peaceful work on human and animal health, agriculture and pharmaceuticals, as for development of BW. Such peaceful work is essential to increase the well-being of mankind throughout the world. This is especially so for developing countries, some of which may be suspected of intentions to use BW. The similarity in know-how and facilities needed for peaceful and aggressive intentions is much greater in considering control of BW than for conventional, nuclear and even chemical weapons. In addition, the BW Convention allows potential BW agents to be produced and transferred by the signatory nations provided the agents are justified for prophylactic and other peaceful purposes (Article I of the BW Convention).

The need for transfer of knowledge and technology for peaceful use has been accepted formally by all signatories to the BW Convention under the provisions of Article X, the two paragraphs of which read:

I. *The States Parties to this Convention undertake to facilitate, and have the right to participate in, the fullest possible exchange of equipment, materials and scientific and technological information for the use of bacteriological (biological) agents and toxins for peaceful purposes. Parties to the Convention in a position to do so shall also cooperate in contributing individually or together with other States or international organizations to the further development and application of scientific discoveries in the field of bacteriology (biology) for the prevention of disease, or for other peaceful purposes.*

2. *This Convention shall be implemented in a manner designed to avoid hampering the economic or technological development of States Parties to the Convention or international cooperation in the field of peaceful bacteriological (biological) activities, including the international exchange of bacteriological (biological)*

agents and toxins and equipment for the processing, use or production of bacteriological (biological) agents and toxins for peaceful purposes in accordance with the provisions of the Convention.

There is a potential conflict between compliance with Article III and with Article X which must be emphasised because of its possible adverse effect on the economic efforts of developing countries. Because the knowledge and technical requirements for aggressive and peaceful intentions are so similar, rigid enforcement of Article III carries the danger of hampering the economic development of the country concerned and thus, contravening Article X. There is little doubt that Article X is uppermost in the minds of the signatories from developing countries (16,17). The happy medium is needed; application of the rules of Article III without compromising efforts to help developing countries with their many problems including fighting infectious disease in humans, animals and plants.

The issues on technology transfer are political (in relation to prevention of BW proliferation without hindering the economic development of nations) and ethical (in relation to the spread of natural knowledge for the benefit of man) rather than scientific which is the subject of this Report. Nevertheless some comment should be made on the feasibility of restricting technology transfer and the present measures adopted by the UK Government. These comments may be of use in any future modification of the present legislation.

2. TRANSFERABLE TECHNOLOGIES AND THE FEASIBILITY OF RESTRICTING TRANSFER WHILE COMPLYING WITH ARTICLE X

The subject is considered under five headings, intangible technology, seed cultures, equipment for large scale production, high containment units and equipment and munitions for developing and testing aerosols. Although separated for discussion, it must be remembered that there is a continuum between intangible and tangible technologies.

2.1 Intangible technology

Microbiology, biochemistry, biotechnology, genetic manipulation and chemical engineering are the basic subjects needed for producing live agents and toxins for BW and also for the peaceful purposes listed above. In the last ten years, there has been an explosion of interest in these subjects throughout the world. Research and teaching in many countries is at a very high level both in amount and calibre. Numerous published journals and textbooks are available to those who wish to learn. The traditional methods of spreading knowledge (publications, international meetings and exchange of students, researchers and lecturers) from established centres of excellence in the more advanced countries to educational and research institutes in less developed countries is proceeding for these subjects as well as for others. Apart from the fact that restriction of this spread of knowledge is academically undesirable and contravenes Article X of the Convention, it could not be made effective. There are too many freely available sources of the relevant knowledge and academic experts in countries enjoying civil rights and freedom of expression would not countenance such restriction. Word of mouth transfer of knowledge is impossible to monitor or stop. Electronic communication and databases are freely available. In addition to these points, a determined person or nation could obtain training in a country that has still not signed the Convention.

2.2 Seed cultures

The transfer of seed cultures of potential BW agents could be restricted by legislation but would it stop a determined transgressor obtaining them? First, transfer of such cultures for peaceful purposes is permitted by the Convention, so how can legitimate and illegitimate requests for cultures be distinguished? Second, seed cultures, especially if they are dried, are small and easily concealed for personal carriage by a transgressor. Third, cultures could be obtained from nations that have not signed the Convention. Finally, field isolates of the most important potential BW agents e.g. *B. anthracis, Y pestis, Brucella spp.* and *Cl. botulinum* can be obtained in most countries from public health and veterinary investigation units. Such isolates would not be the strains already developed for BW (e.g. the 'classical agents'; see chapter 4), but they would provide a threat which could not be ignored. Hence, at best, restriction of transfer of seed cultures could only produce an initial delay in the activities of a determined aggressor but may well interfere with the use of the potential BW agents for peaceful purposes such as teaching courses on infectious disease and vaccine production.

2.3 Equipment for large scale production of microbes and their products

Fermenters, bioreactors, chemostats and large centrifuges, filtration units and freeze driers are needed for large scale production of live microbes and their products for peaceful as well as for BW purposes. Hence, any restriction of supply of this equipment could hinder the economic development of a nation thereby contravening Article X. For example, the equipment may be needed for food processing, brewing or antibiotic production. If restriction is contemplated for a possible transgressor, it should apply only to equipment designed for use with pathogens i.e. fitted with devices to prevent the escape of the contained microbe and product. Even this equipment might be needed for production of vaccines, and restriction would contravene Article X. It would not be difficult for a transgressor to obtain equipment for BW production from non-signatory nations or by transfer from vaccine production in a dual function establishment. Also, a determined aggressor bent on terrorist activity would, if necessary, produce BW agents by a relatively small scale glassware operation without sophisticated safety measures. In summary, restriction of equipment for large-scale production may adversely affect peaceful operations and could only delay not prevent a determined aggressor producing BW agents.

2.4 High containment units

Most potential BW agents should be handled under C4 or C3 conditions of the WHO(18). Hence, restriction of transfer of facilities to work under these conditions, might hinder production of agents. However, it must be emphasized again that a determined aggressor would probably disregard any stringent safety precautions in achieving his objective. Restriction of C4 containment units would have little impact on peaceful purposes. Even in developed nations such units are small in number and used only for exotic microorganisms on rare occasions. There would be only a few requests for transfer of such units which could be easily vetted for legitimacy. On the other hand, restriction of C3 units, particularly small safety cabinets, could result in a diminished capacity to diagnose serious infections (e.g. HIV infection and the increasing number of cases of tuberculosis) in public health and veterinary laboratories. Every request for provision of C3 facilities would have to be scrutinized with respect to these peaceful purposes. If a determined aggressor wished

to bother with safety precautions, he could obtain C3 facilities from or through a non-signatory nation. At best, a delay in BW operations is all that could be achieved by restriction in this area.

2.5 Equipment or munitions for delivering and testing aerosols

Transfer of aircraft spraying equipment, munitions (shells, bombs, rocket heads) containing devices for spreading aerosols (e.g. a screw action discharger) and large chambers for aerosol challenge experiments, i.e. items for obvious military use, could be restricted without repercussion on peaceful activities. Spraying equipment needed for agriculture is largely ground (tractor) based. Requests for spraying equipment for use on aircraft would be relatively few and could he vetted stringently to ensure legitimate use. Aerosol chambers are used in the civilian field e.g. for environmental studies, but not on a large scale. Munitions only have one purpose. Here then, at the delivery level, restriction of technology transfer could be effective in preventing imminent use of BW without a curtailment of peaceful activities.

To sum up this section, restriction of transfer of intangible technology is academically undesirable and virtually impossible to accomplish. Restriction of transfer of seed cultures, large scale production equipment and containment units would curtail peaceful operations and, at best, only delay BW operations. Furthermore, the delay period would not be long when compared with about 10 years that is estimated for nuclear proliferation. Remembering that a determined aggressor could obtain what he needed from third parties or would produce the BW he required using unsophisticated equipment without stringent safety precautions, the delay achieved by the above restrictions would probably be only months for small scale terrorist operations where production of the agent could occur for example in a university laboratory. For larger developments, the delay period would probably be only 1-2 years if the country concerned had rudimentary production facilities and the well known ‘classical agents’ were used. Restriction of means of delivery and testing aerosols of BW agents could be effective in preventing immediate acquisition and use of BW on a large scale and would not adversely affect peaceful operations.

Finally, any administrative office which is set up by a particular nation to restrict technology transfer should either be the same office or have a close liaison with the office dealing with replies to CBMs under the BW Convention (Chapter 5). In turn, the national office should be in close contact with the proposed international office which would receive and analyse the replies to the CBMs (Chapter 5). Such liaison should provide a body of information that will be helpful in judging whether transfers of technology are for peaceful or potential aggressive purposes.

3.RESTRICTION OF TECHNOLOGY TRANSFER BY THE UK GOVERNMENT

On 31 December 1992, in consort with the Australia Group (an informal international forum of nations which exchanges views and coordinates action on export controls against chemical and biological weapon proliferation), the UK Government introduced legislation (The Export of Goods (Control) Order 1992) to control the export of biological materials and equipment that could be used to develop BW. The reasons for this action, the members of the Australia Group and the details of the legislation are set down in a FCO document, Biological Weapons Awareness Raising Booklet; United Kingdom Export Control Legislation (Appendix VII). The main provisions are as follows:

1. The export of many human pathogens and toxins, animal pathogens, genetically modified microorganisms, nucleic acids and genomic libraries and of a variety of equipment capable of use in biological manufacturing, requires a licence from the Department of Trade and Industry (DTI).

2. Exports of these materials to countries of the Australia Group (24 listed) will be allowed under an Open General Export Licence. There is no need for individual export licences but the exported microorganisms or toxins must be recorded for 4 years.

3. Exports of these materials to any other country require an Individual Export Licence from the DTI. The legislation covers all countries not in the Australia Group and about 50 countries of special concern are listed. Failure to comply with this requirement is a criminal offence. In circumstances where there are repeat shipments to the same destination, an Open Individual Export Licence may be granted to avoid the need for repeat applications.

4. There is a `Warning Guideline' document which lists microorganisms, toxins and items such as culture media which are not licensable but may be indications of illegal BW programmes when they are being sought in suspicious circumstances. Exporters are asked to assess carefully orders relating to these items although no guidance is given on how they should be assessed.

5. As an extra precaution there is a 'catch all' paragraph. This places the onus on the exporter to satisfy himself that an enquiry or order from overseas for any microorganism, toxin or equipment (not only for production but also for delivering of aerosols) is for a legitimate end use. If there is any concern or suspicion that the order is intended for use in a BW programme, an application for an export licence must be made.

6. Transfer of intangible technology is mentioned together with the fact that some countries had recently introduced restrictive legislation in this respect. However, concrete proposals to control transfer in this area are not made.

In essence, the threat of proliferation of BW is judged so serious, that very stringent control of relevant exports is now law. For example, a veterinarian in the UK is criminally liable if he sends a culture of *Brucella abortus* to a colleague in Brazil without having a licence.

4. COMMENTS ON THE LEGISLATION ENACTED BY THE UK GOVERNMENT

1. A responsible government cannot ignore the increased threat of proliferation of B W which has been underlined by the findings in Iraq after the Gulf War; and a response to the threat in consort with the Australia Group will be more effective than individual action. It is not made clear in the document whether or not all members of the Australia Group have enacted legislation similar to that adopted by the UK Government.

2. There may, however, have been an over reaction as to how to cope with the threat which could hamper the economic development of some nations. For the reasons given above, the measures set down in the legislation can only delay for a relatively short time a determined aggressor in fulfilling his requirements and they carry a risk of seriously impairing the transfer of technology for peaceful purposes. The over reaction has two aspects, the number of countries affected and the items curtailed.

3. The measures should certainly be applied to those countries which are known from intelligence sources to have a definite interest in producing BW, even if some of them are developing countries. Prevention (more realistically, delay) of BW proliferation should have a higher priority than economic needs in decisions on technology transfer to these nations. It should be the only consideration for developed nations known to be interested in BW especially if they provide a base for terrorist activity.

4. On the other hand, only about 10 countries are known to be interested in BW, yet the countries listed as requiring special attention in the individual licensing procedure number about 50 (Appendix VII). Some of them are developing countries that need economic and technical aid. If they are not known to be interested in developing BW, why should they be subject to the special licensing procedure which may inhibit their economic development? The reasons for placing nations on the list for special attention are not clear nor the procedure that might be adopted in the future for deleting from or adding to the list. In essence, the net may have been spread too widely and could affect adversely not only economic development but increased participation in the BW Convention.

5. The lists of agents and equipment designated for licensing and those in the warning guidelines are extensive and expected to cover most of what is required from production of BW. However, it must be remembered that a determined aggressor would, if need be, produce BW using unsophisticated equipment not on the lists and without safety precautions. Also, the point made in Chapter 4 of the Report applies, namely that it is impossible to list all agents that might be used for BW. It is suggested that biological and toxin agents be defined in general terms, only the 'classical agents' be listed with a few others including vectors for genetic manipulation (see Chapter 4) as examples of what should be licensed, and reliance placed on the 'catch all' paragraph and the common sense of the exporter to ensure that export of relevant agents is licensed. Similarly, the list of equipment could be simplified. Giving less information on both agents and equipment could make things more difficult for potential transgressors. Also, a general definition of biological agents together with the 'catch all' paragraph would take in new developments that might occur in the future.

6. The means of delivery of BW agents i.e. spraying equipment and specialized munitions are not specifically mentioned in the lists of restricted equipment although they are referred to in a general fashion in the 'catch all' phrase. Since restriction of these items is likely to be effective (see first section of this paper), they should have been mentioned specifically under the Orders appertaining to BW.

7. Good public relations will be important in making export control measures work. The cooperation of teachers and researchers in universities and other institutions is required as well as that of people in the microbiological supply industries. This

cooperation would have been made more effective if there had been an open discussion in the document of the difficulties of distinguishing the use of the requested microbes and equipment for peaceful purposes from their potential use for BW operations. Also, a more sympathetic treatment of the problems of the developing countries would have been helpful. Finally, it would have been more diplomatic to have included Article X of the BW Convention as well as Article III in Biological Weapons awareness Raising Booklet: United Kingdom Control Legislation (Appendix VII).

8. Although it is a wise precaution to have a 'catch all' paragraph, placing the onus on the exporter of finding out (and hence the blame if things go wrong) whether or not potential agents might be used for the development of BW is wrong. Clearly under the 'catch all' paragraph, an exporter should inform the government authority of any suspicious request (e.g. a microorganism or toxin not included in the official lists, see paragraph 5) but the onus of taking the matter further should be on the government authority because they have ways and means of verifying suspicious activity not available to the exporter. The cooperation of the exporter is needed to provide the authority with all relevant information but the responsibility for action should be carried by the authority. If the onus lies with the exporter, it may well lessen his enthusiasm for selling his wares to developing nations for peaceful purposes which is against the spirit of Article X. The best way forward is for the authority to achieve a collaboration with exporting companies whereby unusual requests are referred to the authority for investigation. This will provide the latter with information about possible proliferation. Such monitoring of possible illicit activity is important. If an exporter is put off by the fact that he must bear the onus of proof of illicit activity, the amount of information reaching the authority in this way will be reduced.

9. It is not clear in the document whether sanctions will be used against third parties that helped in illicit transfer of technology.

10. It would be unwise for the Government to attempt to restrict the transfer of intangible technology by any means. It would contravene Article X of the BW Convention and would not be successful. Furthermore it might lead to controversy if universities, research organizations and learned societies were asked to engage in such a venture.

11. It is open for the Government to refuse entry to nationals from those countries, for which there is doubt about full compliance with the BW Convention, and who are seeking contact with UK institutions doing work relevant to BW. This would be a more straight forward procedure than trying to persuade universities and research organizations to deny places to such people without giving the reason.

12. One possible approach to a more liberal method for the UK Government to deal with technology transfer would be to connect the level of restriction to whether or not a nation had signed the BW Convention. Signatories could be treated as for members of the Australia Group with regard to transfer of tangible and intangible technology provided there was no evidence from intelligence sources of potential interest in BW. This measure might encourage more nations to sign the BW Convention.

An overall impression of the government legislation is that at best only a short delay in proliferation can be achieved and a much simpler system less inhibitory to developing nations would be adequate to restrict transfer to known potential transgressors.

5. SUMMARY OF CONCLUSIONS

1. Technology transfer in relation to development of BW is an important issue because of the increasing danger of proliferation.

2. The BW Convention attempts to prevent technology transfer in relation to aggressive purposes (Article III) and to encourage it for peaceful purposes (Article X). There is a conflict between the two because the knowledge and equipment needed are the same for both. Rigid enforcement of Article III could inhibit economic development in some nations.

3. On 31 December 1992, the UK Government enacted detailed legislation to restrict export of BW related materials and they are contemplating measures for restriction of transfer of intangible technology (Appendix VIII).

4. Restriction of transfer of intangible technology would be undesirable because of its normal use in medicine and agriculture. Also it is virtually impossible to accomplish. It would contravene Article X of the BW Convention and would hinder efforts to increase transparency between nations.

5. Restriction of transfer of seed cultures, large scale production equipment and containment facilities can, at best, achieve only a short delay (1-2 years) in development of BW, with the risk of curtailing peaceful operations in developing countries.

6. Restriction of means of delivering and testing aerosol BW agents could be effective in preventing immediate acquisition and use of BW without adversely affecting peaceful operations.

7. A responsible government cannot ignore the increased threat of proliferation of BW but there may have been an over reaction in the present legislation (Appendix VII) as to how to cope with the threat, which could hamper the economic development of some nations. The over reaction has two aspects, the number of countries affected and the items curtailed.

8. A determined aggressor will obtain BW if he needs them. Only a short delay in proliferation (1-2 years) is achievable because of the widespread availability of the knowledge and technology involved. This delay could be attained by a much simpler system than the present legislation which is potentially inhibitory to developing nations. The restrictive measures should be concentrated on those countries known to be interested in developing BW. The lists of restricted items should be reduced and the ban on delivery systems emphasised.

8. INTERNATIONAL SCIENTIFIC COOPERATION

The activities of VEREX (Chapter 6) over the past two years have demonstrated that experts from signatory nations can cooperate on scientific and related matters for the common good when an important issue such as verification is concerned. Also, on a smaller scale, the 24 members of the Australian Group (Chapter 7) have shown such cooperation in attempting to control exports of materials related to CW and now BW. This type of international cooperation should be extended to other areas.

1. INVESTIGATION OF THE ALLEGED USE OF BW

The present discussions of VEREX may result, at the next Review of the BW Convention (1996), in setting up a permanent organization for verification of compliance with the obligations set out in the Convention. In general terms, this organization will probably consist of a central administrative office, teams of on-site inspectors and an internationally agreed committee to assess reports. Inherent in its work will be increasing cooperation between scientific experts in different countries e.g. in agreeing methods for identification of BW agents (Chapter 6). This type of organization could also deal with incidents of alleged use of BW. Indeed, it could be argued that this was an integral part of a comprehensive verification procedure. In the past, alleged use of BW such as the Sverdlovsk and 'yellow rain' incidents were never investigated fully (Chapter 3) because, amongst other things, a relevant international organization was lacking. The international body could only investigate incidents if the country concerned allowed access to the area where the alleged use of BW took place. Probably this would not have occurred on the two previous occasions. Assuming, however, that political good will was forthcoming, or the UN could impress its will on a recalcitrant nation (as for Iraq), what are the administrative and scientific requirements for such investigations? They would be similar to those required for a situation arising during verification procedures when indications of intent to develop BW had been discovered (Chapter 6). First, there would be an on-site inspection by an expert team. This team could use some of the internationally validated methods of detecting BW agents which are suggested in section 4 of Chapter 6. Medical examinations would be important to ascertain the clinical effects and pathology of the disease. If allowed politically and ethically, the collection of blood from casualties and survivors in the areas for antibody analysis would be especially important. Following the on-site inspection, there would have to be base laboratory confirmation of the on-site findings and possible extensions of the investigations with further analysis of the results. Two independent laboratories should be involved. Finally, the reports would go for judgment to the internationally agreed senior committee. The organization and particularly the administrative office should have close links with appropriate sections of the WHO; and it is possible for some incidents, joint action could be taken which might cut costs.

The procedure described could also be applied to retrospective investigations of alleged use of BW. For example, an unusual epidemic of anthrax occurred in man and cattle in Zimbabwe in 1978-1980 (32). The epidemic was large and occurred in areas where outbreaks of anthrax are usually small and infrequent. It has been suggested that the epidemic may have been the result of deliberate use of anthrax as a BW against African-owned cattle in the final months of the Zimbabwe civil conflict (32). A study of this incident, sanctioned by the present Zimbabwe Government, is now being planned (An announcement by the Council for Responsible Genetics, Cambridge Mass. USA, 3 February

1993). Obviously an important scientific aspect of this study should be characterization of the genetic structures of the strains of *B. anthracis* collected in Zimbabwe at the time of the incident and comparison of these structures with those of: a). strains found previously in southern Africa, particularly in the area concerned; and b). strains that are found elsewhere in the world, particularly those that were weaponised in the past. The methods for making these comparisons are well known (Chapter 6). Also, the examination of blood of people in the area who survived the epidemic for antibodies to various strains of *B. anthracia* might be revealing. An international organization like that suggested above would not only be able to deploy the requisite expertise, but its final conclusions would carry more weight with the international community than those of less universally accepted bodies. Retrospective investigations of this type may deter potential users of BW. They would realize that there was a possibility of being found out later on, if and when a political change allowed access and appropriate investigations.

2. DEALING WITH ACTUAL USE OF BW

Article VII of the Convention states:

> *Each State Party to this Convention undertakes to provide or support assistance in accordance with the United Nations Charter, to any Party to the Convention which so requests, if the Security Council decides that such Party has been exposed to danger as a result of violation of the Convention.*

If BW were used, an already existing internationally agreed verification organization of the type described above would be able to supply immediate expert advice and help to identify the BW agent concerned. Also, given sufficient finance, its remit could be widened to include treatment of casualties, prevention of further spread of the agent, decontamination of land and water and if necessary destruction of BW stocks. If the remit was widened to include these items, some thought would have to be given to membership and training of the 'fire brigade' units. Their services would be required only on rare occasions so they could consist of inspectors who would spend most of their time on verification of the Convention.

3. BIESENTHAL VACCINE INITIATIVE

At Biesenthal (Germany) in September 1992 a meeting was held of experts from Australia, France, Germany, Hungary, India, Peru, Russia, Sweden, USA and the UK with observers from WHO, the UN Industrial Development Organization (UNIDO) and the UN Office for Disarmament Affairs to discuss a 'Vaccines for Peace' programme suggested by Professor E. Geissler. The essential aim is to divert R&D effort from BW to production of vaccines against diseases that may have connections with BW but are general problems of public health in developing countries. The proceedings of the meeting and the agreements reached are summarized in Appendix VIII. The intention is to work in conjunction with WHO, UNIDO and other international organizations. A steering committee has been formed. One of its remits is to consider the existing and emerging diseases in developing countries for which, improved or new vaccines are most required.

This is an ambitious scheme requiring large and continuing financial support. The sources of this support are not yet clear. Nevertheless, the scheme should be welcomed and encouraged not least because it addresses Article X of the BW Convention and therefore

should be popular with developing countries. If finance becomes available, it would be prudent to concentrate on a vaccine for one important disease and make it a success before moving on to others; dispersal of funds over numerous projects would be mistaken. Overall, it would be better to stress that the effort is directed to diseases of general public health importance rather than those with BW connections.

4. MAKING THE INTERNATIONAL SCIENTIFIC COMMUNITY AWARE OF THE DANGER FROM BW

National bodies, such as the Royal Society and other national academies, and international organizations such as the International Council of Scientific Unions, should be encouraged to bring to the notice of the scientific community at large, the increasing danger of BW and the problems of control. The danger is not as great as that from nuclear weapons but it is formidable.

It is hoped that international cooperation by experts started at VEREX will expand along these lines. Contact between relevant staff of different nations would increase automatically thereby fulfilling CBM, D (Chapter 5). Mutual confidence and respect would follow leading to increased transparency in all operations. Better control of BW would be the overall result.

5. SUMMARY OF CONCLUSIONS

1. The cooperation of international experts on verification issues in relation to control of BW should be extended. Mutual confidence and respect would follow and hence greater transparency.

2. If an international organization was established at the next Review conference (1996) for the purposes of verification, its scope could be widened to investigate instances of alleged use of BW and, possibly, to render help in areas where BW had been used.

3. The Biesenthal Vaccine Initiative is welcomed, especially if it concentrates on production of vaccines against diseases of general public health importance in developing countries.

9. CONCLUDING REMARKS

The objective of this study was to examine the scientific aspects of control of BW with a view to making suggestions as to how the present measures adopted under the BW Convention might be improved.

Recommendations that could lead to improvements in control have emerged for all five of the aspects that were chosen for detailed consideration. They are summarized at the end of each chapter. Some of the ideas are novel, such as those concerned with remote and near-site surveillance of potential high risk areas (Chapter 6). Others arose from taking a realistic view of the capabilities and limitations of existing technologies. Under this category are the recommendations that verification should be based on the unequivocal identification of a few, the 'classical', agents as an indicator of possible BW activity; and that the simplest, cheapest and most effective method of providing on-site identification at high sensitivity levels is laboratory use of ELISA and PCR (Chapter 6). Overall the attitude has been to make control procedures as simple as possible, for example the suggested redesign of the reply forms for the CBMs.

The Report provides a detailed discussion of important aspects of the subject for those persons specifically interested in verification and other matters of control presently being contemplated by the international community.

It is hoped that the Report will prove useful for government officials who will be engaged in the deliberations of VEREX and then the 1996 Review of the BW Convention. When the CW Convention is reviewed at the end of five years, the section of this Report on toxins (Chapter 4) might be helpful to people concerned. Finally, the comments on the technology transfer (Chapter 7) may be useful to government officials in judging the issue of transfer of intangible technology and in any future revision of the present legislation governing transfer of tangible technology.

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