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Survey of DOE Facilities: Impact of Potential Measures to Enhance Compliance with the Biological and Toxin Weapons Convention

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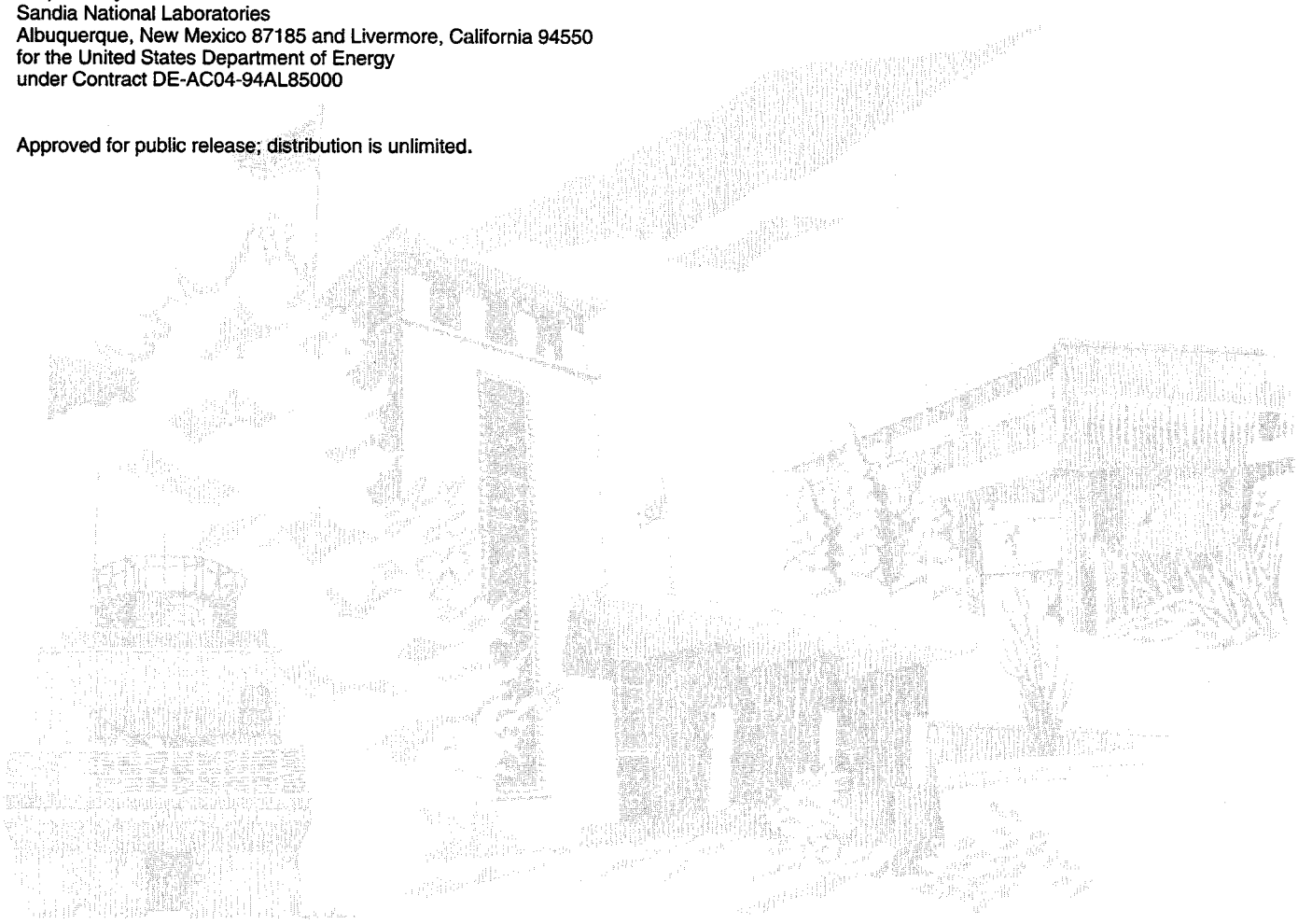

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Survey of DOE Facilities:
Impact of Potential Measures to Enhance Compliance with the Biological and Toxin Weapons Convention

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Abstract

The Biological and Toxin Weapons Convention (BTWC) is a multi-national agreement that seeks to forestall the stockpiling of biological materials in types or quantities not justifiable for protective, prophylactic, or other peaceful purposes. The convention has no verification regime to monitor compliance, but the Parties to the Convention are mandated to write a legally binding monitoring regime for the BTWC that will supplement existing confidence building measures. The scope of this regime is not yet clear, but may include a series of on-site measures designed, to varying degrees, to help enhance compliance with the Convention. DOE National Laboratories may be subject to declaration and/or inspection under the monitoring regime because of the extensive biotechnology work now performed at those sites. This study surveys major DOE sites to analyze the effects on biotechnology programs of measures on which could be agreed in the future, and is intended to assist decision makers as the U.S. Government develops its approach to the negotiations under the Convention.

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Acronyms

ANL	Argonne National Laboratory
BNL	Brookhaven National Laboratory
BTWC	Biological and Toxin Weapons Convention
CRADA	Cooperative Research and Development Agreements
CWC	Chemical Weapons Convention
DOE	Department of Energy
DOE/NN	The DOE Office of Nonproliferation and National Security
FFRDC	Federally Funded Research and Development Center
INEL	Idaho National Engineering Laboratory
ITRI	(Lovelace) Inhalation Toxicology Research Institute
IWG	Interagency Working Group
LANL	Los Alamos National Laboratory
LBL	Lawrence Berkeley Laboratory
LLNL	Lawrence Livermore National Laboratory
NREL	National Renewable Energy Laboratory
NTI	National Trial Inspection
OHER	Office of Health and Environmental Research
ORNL	Oak Ridge National Laboratory
PNL	Pacific Northwest Laboratory
SNL	Sandia National Laboratories
SPECTRE	Spectroscopic Excitation and Classification of Trace Effluents
VEREX	Verification Experts Group (BTWC ad hoc group)

Survey of DOE Facilities:

Impact of Potential Measures to Enhance Compliance with the Biological and Toxin Weapons Convention

Executive Summary

The Biological and Toxin Weapons Convention (BTWC) seeks to forestall the stockpiling of biological materials in types or quantities not justifiable for protective, prophylactic or other peaceful purposes. The Parties to the Convention are now considering details of a legally-binding monitoring regime for the BTWC, which goes beyond existing confidence building measures. The scope of this regime is not yet clear, but may include a series of on-site measures designed, to varying degrees, to help enhance compliance with the Convention.

The Department of Energy (DOE) funds a wide ranging program in fundamental research and development in biology and biotechnology at several of its national laboratories, and also sponsors research in academic institutions. It is therefore highly likely that some DOE-sponsored programs may be included in a monitoring regime for the BTWC. Depending on the nature of the regime, the impacts on DOE programs could be significant. The DOE Office of Nonproliferation and National Security (DOE/NN) requested a survey of DOE facilities, focused on unclassified programs, to study potential impacts.

Following a mandate from the Third Review Conference of the BTWC held in 1991, a group of multinational experts recently defined and considered a group of off-site and on-site measures. These measures served as the basis for the impact survey. Eight DOE National Laboratories, and one other DOE-sponsored facility participated in a survey to assess the impact of these measures on each facility. Impacts were graded based on the subjective responses returned from experts at each of the DOE sites.

Most experts felt that off-site measures, including declaration of activities at a facility and technical information exchange, would be easily tolerated. On-site measures, including some activities traditionally associated with intrusive monitoring for arms control treaties, could in many circumstance be extremely costly. Most of these costs center around commercially valuable data, which are part of Cooperative Research and Development Agreements (CRADAs). CRADAs make up a significant and increasing portion of funding at DOE biotechnology facilities. Participants from these sites are very concerned about their role in improving United States industrial competitiveness as directed by the President, and in maintaining their market competitiveness as partners with major R&D corporations. Protection of information is vital, in the opinion of facility participants.

Other important conclusions for the survey are

- Potential impacts vary from laboratory to laboratory which, suggests strongly that specific characteristics of research at each site determine the nature and extent of effect of measures, particularly on-site measures. Further, impacts of potential BTWC measures on biotechnology programs are likely to be different than the effects of Chemical Weapons Convention (CWC) verification on the chemical industry.

- With sufficient screening of documents, DOE sites can comply with most of the requirements of off-site measures as outlined in the Verification Experts (VEREX) descriptions. However, even in the case of off-site measures, preparation of appropriate documents may be costly due to the need to remove proprietary information.

- For some DOE sites that currently have small or absent site security, significant expenditure may be required to escort visitors from an international organization such as one carrying out compliance measures for the BTWC. Safety and protection of business information are the main concerns associated with escorting.

- DOE-sponsored laboratories, other than national laboratories (such as the Inhalation Toxicology Research Institute in Albuquerque, NM), maintain specialized technologies, such as aerosol technology and disease pathogenesis, which may be of relevance to the BTWC and measures under consideration to strengthen the Convention.

As the U. S. Government Interagency Working Group (IWG) considers the details of measures that it will sponsor in the negotiations in the BTWC, DOE biotechnology experts can provide important technical opinion on the impact of monitoring at DOE sites. In addition, DOE experts can help to educate negotiators on the benefits and limitations of potential measures. These valuable resources in DOE sponsored biotechnology programs should be exploited during the negotiating process.

Survey of DOE Facilities:

Impact of Potential Measures to Enhance Compliance with the Biological and Toxin Weapons Convention

Overview

The Biological and Toxin Weapons Convention (BTWC) seeks to forestall the stockpiling of biological materials in types or quantities not justifiable for protective, prophylactic or other peaceful purposes. At the time of its entry into force in 1975, the BTWC had no verification protocol as States Parties could identify no satisfactory means to monitor compliance with the Convention. In subsequent Review Conferences in 1986 and 1991, the Convention adopted a series of annual reporting requirements as confidence building measures. Although compliance with these requirements has been less than universal, there was agreement that additional means should be sought to strengthen the Convention. Thus, the signatories to the Convention are considering the possibility of a monitoring regime for the BTWC that goes beyond existing confidence building measures. Although the scope of the regime is not yet determined, it is conceivable that during the negotiations to craft a regime, components could include inspections similar to those of other arms control treaties, such as the recently completed Chemical Weapons Convention (CWC). A careful cost-benefit evaluation of proposed measures for the BTWC monitoring regime will likely take place within the U. S. Government. In preparation for this work, the Department of Energy wishes to explore the impact of potential monitoring measures.

The Department of Energy funds a wide ranging program in fundamental research and development in biology and biotechnology at several of its national laboratories, and also sponsors research in academic institutions. It is therefore highly likely that some DOE-sponsored programs may be captured by a monitoring regime for the BTWC. Depending on the nature of the regime (which would include, among other things, the intrusiveness of the regime), the impacts on DOE programs could be significant.

The DOE Office of Nonproliferation and National Security (DOE/NN) requested a survey of DOE facilities, which focused on unclassified programs, to study potential impacts. The scope of this study is to (1) identify and describe biology and biotechnology programs at DOE facilities, including nature of work, types of projects and the approximate funding for these programs and (2) obtain as detailed as possible a description and analysis of the possible impacts of a wide range of measures that *could* be included in a monitoring regime for the Biological Weapons Convention.

It is critical to establish a context for evaluating DOE funded work that may be of relevance to a monitoring regime for the BTWC; thus there are several important caveats in defining the scope of this work, and in interpreting the data obtained. First, it is difficult to precisely define "biological programs" or "biotechnology programs" from both technical and programmatic (or funding) points of view. Biotechnology may encompass an extremely large range of activities or projects, and may be funded from

numerous sources. The Congressional Office of Technology Assessment broadly defines biotechnology as "any technique that uses living organisms (or parts of organisms) to make or modify products, to improve plants or animals, or to develop microorganisms for specific use."[1] The DOE currently funds work ranging from fundamental biology (e.g. molecular biology and genetics) to applied biotechnology. This latter category includes applied genetics, such as the Human Genome Project, but also under a broad definition of "biotechnology" includes environmental remediation work, such as bioremediation – the use of microorganisms to effect clean up of polluted sites. Clearly some of these programs are of greater relevance to the BTWC than others. We believe that a narrow definition of biotechnology, focusing on fundamental research and development rather than all applications of biotechnology, would be of greatest interest to a putative BTWC regime. Thus, our interests in this survey are on a somewhat restricted definition of biotechnology: fundamental, biologically-based research and development, which is defined in greater detail below.

Second, it is not possible to know with any degree of precision the detailed description of a measure or measures that might eventually be part of a monitoring regime for the BTWC. Only a broad overview of measures and rather loose descriptions of a regime can be determined at this time. There are many potential combinations of measures in a regime, and clearly some specific combinations of measures may have greater impact than others. Therefore, in surveying DOE facilities for potential impact, measures were considered individually and in combination; further, only broad definition were provided. More detail on the description of measures is provided later in this report.

Finally, there are many conceivable impacts at a DOE site for any given measure that seeks to assist in monitoring compliance with the BTWC. We chose to focus on three major areas: the costs of site preparation; the costs for security; and impact on scientific research, including collaborative research with industry. Some of these impacts can be described quantitatively (albeit approximately); others only qualitatively. Analysis of data can vary depending on the inclusion of qualitative impacts. We chose to preserve as much of the qualitative data as possible as it represents the range of the best expert opinion available to provide to decision makers who wish to understand the potential risks and benefits of measures designed to strengthen the BTWC.

The body of this report is organized into three major sections. The first provides a description of biotechnology programs sponsored by the DOE that we believe may be of relevance in a regime designed to strengthen compliance with the BTWC. This section summarizes programs at seven major DOE national laboratories (Lawrence Livermore, Lawrence Berkeley, Argonne, Los Alamos, Oak Ridge, Brookhaven and Pacific Northwest) and at one single-program laboratory – the Lovelace Inhalation Toxicology Research Institute. The nature of the projects, funding levels, and a breakdown of work for DOE and work for non-DOE entities are provided. This section also provides a

[1] U.S. Congress, Office of Technology Assessment, Commercial Biotechnology: An International Analysis. OTA-BA-218 (Washington, DC: U.S. Government Printing Office, January 1984), page 3.

summary of the recent efforts in the BTWC to explore specific measures that might be undertaken to improve compliance with the Convention. This section includes an overview of the work of a group of technical experts mandated by the Convention to study the feasibility of verification for the BTWC, and also detailed descriptions of measures considered by the experts group.

The second section summarizes the results of the survey of the DOE facilities in which participants were asked to evaluate the impact of 21 potential verification measures (derived from the BTWC technical experts group noted above) on scientific and research activities. Results are summarized by site, and overall analysis is provided.

In the final section, overall conclusions are provided.

1. Introduction

1.1. Historical Context

The Biological and Toxin Weapons Convention (BTWC), a multinational agreement involving over 130 States Parties, is formally known as the "Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction." It was signed by the United States in 1972 and entered into force in 1975. The history of the BTWC begins with the Geneva Convention of 1925, which outlaws the use of both chemical and biological weapons on the battlefield. The Geneva Convention did not prohibit the *stockpiling* of these materials, as many parties to the Convention wished to be able to retaliate in kind if deterrence failed. Thus, stocks of chemical and biological weapons were held by several nations after World War I.

During the period from 1932-1937, unsuccessful attempts were made to craft an agreement to prohibit stockpiling of biological and chemical weapons, but it was not until 1962 that the Eighteen-Nation Disarmament Committee again took up the question of eliminating stocks of these materials for weapons purposes. Progress was delayed for many years over whether or not there should be a linkage between biological and chemical weapons, or whether their elimination should be considered separately. The United States and the United Kingdom were of the view that there were enough technical differences between these classes of weapons to justify separate consideration. The Soviet Union and its allies insisted that they be considered together. There the matter stood until 1971 when the Soviets agreed to consider a 1969 British draft convention on the elimination of biological weapons. Negotiations proceeded rapidly from that point, culminating in signing among the three depository nations (U.S., U.K., U.S.S.R.) on April 10, 1972. It is useful to note that much of the impetus to reach a solution to the linkage problem was provided in 1969 by then President Nixon's decision to unilaterally destroy the United States stocks of biological weapons agents and associated delivery devices.

The major thrust of the BTWC is summarized in Article I of the Convention which states:[2]

> "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."

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[2] United Nations. Final Report of the Special Conference to the Biological Weapons Convention, Geneva, September 1994.

Other articles in the Convention deal with: consultation mechanisms should any problem arise[3]

> "in relation to the objective of, or in the application of the provisions of, the Convention;" facilitation of peaceful exchange of biotechnology; and passage of domestic legislation in States Parties to prohibit the "development, production, stockpiling, acquisition, or retention of the agents, toxins, weapons, equipment and means of delivery specified in Article I of the Convention."

Notably absent in the Articles of the BTWC are provisions for monitoring compliance with the Convention. Critics identified the absence of verification mechanisms as a major shortcoming in the regime. The United States had taken the view during the negotiations to establish the Convention that the BTWC was, at the time, technically impossible to verify due to the inherent dual-use nature of biological materials and techniques used in bioprocessing. Further, the United States argued that the ease of production of biological materials and the ubiquity of technology for so doing rendered impossible any confidence in identifying non-compliance in a timely fashion. The United States believed, however, that BTWC was an important international norm, and thus had value despite the absence of a verification protocol.

Concern over this issue slowly developed during the two decades after completion of the Convention. Finally, despite expressions of reluctance on the part of the United States, the Third Review Conference in September 1991 agreed to establish an Ad Hoc Group of Governmental Experts to identify and examine potential verification measures, from a scientific and technical standpoint, to strengthen the effectiveness and improve the implementation of the convention. This group of verification technical experts became known as VEREX (for VERification EXperts), and received a mandate to evaluate potential verification measures, though not to write a verification regime. Measures were to be evaluated against the following criteria:[4]

"• the strengths and weaknesses based on amount and quality of information provided by the measures;
- the ability of measures to differentiate between prohibited and permitted activities;
- their ability to resolve compliance ambiguities;
- technology, material, manpower, and equipment requirements to carry out the measures;
- financial, legal, safety and organizational implications; and
- impact on scientific research, cooperation, industrial developments, and other permitted activities, as well as implications for confidentiality of commercial information."

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[3] *Ibid.*

[4] United Nations. Ad Hoc Group of Governmental Experts to Identify and Examine Potential Verification Measures from a Scientific and Technical Standpoint - Report. Geneva, 1993.

The VEREX group met four times between April 1992 and September 1993 and identified 21 potential measures, listed in Table 1, which are divided between on-site and off-site measures.

Table 1. Potential Verification Measures Identified by the BTWC Ad Hoc Group of Verification Experts

Off-site Measures

Information Monitoring

1. Surveillance of publications
2. Surveillance of legislation
3. Data on transfers, transfer requests and production
4. Multilateral information sharing

Data exchange

5. Declarations
6. Notifications

Remote Sensing

7. Surveillance by satellite
8. Surveillance by aircraft
9. Ground-based surveillance

Inspections

10. Sampling and identification
11. Observation
12. Auditing

On-site Measures

Exchange visits

13. International arrangements

Inspections

14. Interviewing
15. Visual inspections
16. Identification of key equipment
17. Auditing
18. Sampling and identification
19. Medical examination

Continuous monitoring

20. By instruments
21. By personnel

VEREX described the measures in some detail, and addressed the mandate criteria to varying extents for each of the 21 measures. Table 2 is a summary of the description of the measures agreed by the VEREX group.

Table 2. Description of the 21 VEREX Measures
(Note: VEREX experts referred to the "BTWC" as the "BWC")

Off-Site Measures

Measure	Description
Surveillance of publications	Computer-assisted scanning and analysis of publicly available printed matter, including media reports, with special attention to scientific literature related to activities in biological sciences.
Surveillance of legislation	Collection and analysis of information with regard to national legislation that exists covering obligations under the BWC or other areas of interest
Data on transfers/production	Collection and analysis of national export and import data, available or specifically requested, government and industrial production statistics, culture collection records and similar information. Standards for reporting of information will have to be defined.
Multilateral information sharing	The use of any voluntary international provision of exchange of information on medical, veterinary, agricultural, environmental safety standards, defense and waste management issues, etc. relating to materials and activities of potential relevance to the BWC. Such information sharing on a voluntary basis may or may not have an agreed standard for the nature of the information to be provided.
Declarations	Mandatory, periodic reporting on a regular basis of information considered to be of relevance to the BWC. The nature of the events/items/facilities to be declared has yet to be fully defined.
Notifications	Notifications are considered to be a subset of declarations, concerned with the reporting of new or unforeseen events or forecast of events in order to pre-empt compliance concerns.
Surveillance by satellite	Use of orbiting artificial bodies to detect, measure or identify some property of an object of interest without actually coming into physical contact with the object.

Surveillance by aircraft	As described in satellite surveillance, except that an airborne platform is employed.
Ground-based surveillance	Surveillance of a site of interest at some agreed perimeter surrounding a site or many kilometers distant either by remote sensing or by visual inspection
Sampling and ID	Obtaining environmental samples (soil, air, water) in the area of a declared or undeclared facility without penetrating its boundary.
Observation	Monitoring a site to get a sense of activities being carried out in the facility and also to understand the external characteristics of the facility.
Auditing	Critical examination, outside of a facility boundary, in accordance with agreed standards and criteria, of documentary records, electronically held data and manuals to assess consistency of recorded material with declared purposes and permitted activity.

On-site Measures

Measure	Description
Exchange visits	Visits of experts arranged for scientific purposes by one country to comparable facilities of another country. Exchange visits need not be restricted to declared facilities.
Interviewing	Interviewing of personnel to gain information about the nature, scale and scope of the activities of a site in order to assess the overall function of a site.
Visual inspections	General overview of site, facilities, equipment, materials and the degree of protection, safety measures, and the peaceful activities which are being carried out.
ID of key equipment	Directed at confirming a facility's declaration and help to ensure that the equipment is not used for prohibited activities.
Auditing	Critical examination, within a facility boundary, in accordance with agreed standards and criteria, of documentary records, electronically held data and manuals to assess consistency of recorded material with declared purposes and permitted activity.

Sampling and ID	Obtaining environmental samples (soil, air, water) within a declared or undeclared facility; may include process sampling, surface samples, with identification taking place in appropriate laboratories.
Medical Examination	May include one or more of: Auditing medical and occupational health records of a facility's work force; examination of recent and past cases of disease; taking and analyzing body fluids and other clinical materials; surveying immunological status of work force compared to epidemiological background data.
Continuous monitoring	Activity conducted on a continuous basis using devices or instruments with the specific purpose of monitoring ongoing processes, included process parameters, occurring in key equipment of a particular facility, storage rooms and/or testing areas.

This summary of the measures indicates, in some instances, the difficulty VEREX participants had in arriving at precise descriptions and definitions. Indeed, the ambiguity in some of the descriptions left some VEREX participants dissatisfied. From the technical standpoint, ambiguity meant that evaluation of the measures against the prescribed criteria was a difficult task at best.

VEREX was designed to be an effort at technical consultation for the States Parties to the BTWC, but political forces were evident during the work of the group. One example is the failure of the VEREX group to actually define "verification" beyond the guidance provided in the mandate, yet participants continued the long standing arguments over the verifiability of the BTWC. For some countries, VEREX was viewed as an opportunity to create a further, definitive mandate to draft a verification regime. For other participants, VEREX provided a forum to introduce other agendas, such as the need to provide technical assistance to developing nations. And for still other States Parties, VEREX afforded the chance to debate the enormous technical complexities associated with the description and examination of each of the 21 measures.

Thus, the final report of VEREX reflects some of the ambiguity inherent in its work. The report states that "from the scientific and technical standpoint, that some of the potential verification measures would contribute to strengthening the effectiveness and improve the implementation of the Convention." VEREX also concluded that "some combinations of some potential verification measures, including both off-site and on-site measures, could provide information which could be useful for the main objective of the Biological Weapons Convention." The VEREX report makes no statement on whether or not verification is achievable, though it does recognize that verification would be desirable, if it could be achieved.

Further action was left to a Special Conference held during October of 1994. The Special Conference welcomed the VEREX report and agreed to establish a new Ad Hoc Group, open to all States Parties. According the final report of the Special Conference:

> "The objective of this Ad Hoc Group shall be to consider appropriate measures, including possible verification measures, and draft proposals to strengthen the Convention, to be included, as appropriate, in a legally binding instrument, to be submitted for the consideration of the States Parties. In this context, the Ad Hoc Group shall, *inter alia* consider:
>
> - Definitions of terms and objective criteria such as lists of bacteriological agents and toxins, their threshold quantities, as well as equipment and types of activities, where relevant for specific measures designed to strengthen the Convention;
>
> - The incorporation of existing and further enhanced confidence building and transparency measures, as appropriate, into the regime;
>
> - A system of measures to promote compliance with the Convention, including, as appropriate, measures identified, examined and evaluated in the VEREX report. Such measure should apply to all relevant facilities and activities, be reliable, cost effective, non-discriminatory and as non-intrusive as possible, consistent with the effective implementation of the system and should not lead to abuse;
>
> ... Measures should be formulated and implemented in a manner designed to protect sensitive commercial proprietary information and legitimate national security needs.
>
> Measures should be formulated and implemented in a manner designed to avoid any negative impact on scientific research, international cooperation and industrial development."

At this time, it is unclear whether or not the Ad Hoc Group will seek to establish an extensive monitoring infrastructure (along the lines of the recently completed Chemical Weapons Convention), or whether its goals will be more modest.

The Ad Hoc Group held an organizational meeting in January 1995 to outline the plan to proceed with drafting a regime for the BTWC. It was decided that future decisions will be made by consensus, and there is a desire on the part of most participants to complete work on the drafting in time for the meeting of the Fourth Review Conference to be held in September 1996. Individual States Parties must now consider the scope of the regime, the acceptability and value of specific measures, and the possibility of introducing new measures as part of the drafting process. Thus, the U.S. Government is beginning to study measures designed to strengthen compliance with the Convention, and will probably propose a specific combination or list of measures, which comprise a protocol that is consistent with the need to balance benefits and costs as outlined in the final report of the States Parties. Such considerations are complex, and each executive agency within the U.S. Government has its own particular set of equities in the process. In particular, facilities with the Department of Energy could be subject to monitoring procedures under the protocol, depending on the yet-to-be-determined objectives and scope of the regime. Thus, the DOE has undertaken a survey of DOE facilities and sponsored programs that might be of relevance to the BTWC – including biotechnology programs funded by the DOE. The following subsection of this report summarizes biotechnology-based work at DOE facilities.

1.2. Description of DOE-Sponsored Biotechnology Programs

The Department of Energy sponsors a wide range of biotechnology programs at its national laboratories, and, in addition, sponsors biotechnology research at universities throughout the United States. In addition, DOE national laboratories carry out biologically-based work for other federal agencies (such as the National Institute of Health), and they also contract with industry under Cooperative Research and Development Agreements (CRADAs).

There is no universally agreed definition of biotechnology. In this report, we have defined biotechnology to be comprised of three main fields that are likely to be of relevance to the Ad Hoc Group, which is charged with evaluating measures to strengthen the BTWC. These fields are bioprocessing, biomedicine, and biologically-based environmental research. Based on this definition, it is also possible to obtain reasonable estimates of the funding for biotechnology at DOE facilities.

Bioprocessing uses living organisms or their viable fraction to produce new products, and is the critical link between fundamental science and innovative industrial application. A major emphasis in bioprocessing is on systems that can produce fuels and chemicals economically from renewable feedstocks including the use of appropriate waste materials. Bioprocessing of coal and petroleum, as well as systems for removal of process pollutants, are also important aspects of this field of biotechnology.

Biomedicine is directed at providing instrumentation for biomedical application (including image processing, biosensors, and other diagnostics) and also improved understanding of human genetics. Genome structure/function relationships and the basis for a number of hereditary diseases are a prime focus of this research. Other techniques in DNA analysis are also lumped here.

Environmental biotechnology focuses on the application of molecular biology to environmental issues. Some activities include bioremediation for decontamination of organic materials and heavy metals, development of biomarkers that reflect changes in the environment due to contamination, and modeling of global climatic change.

Over the past decade, DOE national laboratories have dramatically expanded work in biological sciences. Some of this expansion was driven by immediate programmatic needs within the DOE complex, such as environmental cleanup where bioremediation is seen to play an important potential role. In addition, the scientific resources within DOE laboratories are applicable to problems in areas such as molecular biology and medicine, and these resources are often uniquely located in DOE facilities. As the national laboratories have begun to expand from their traditional roles in national security and fundamental research into new domains, such as assisting national competitiveness, biotechnology is a natural area of growth.

In the area of bioprocessing, DOE laboratories are currently pursuing programs such as bioconversion of waste, biomass separation, biofilters, and metabolic engineering. In environmental engineering, biotechnology-based programs include geobiology, oceanography, soil and water remediation, isolation of radioactive waste, biomarkers of environmental contamination, and subsurface microbiology. Biomedical applications and research constitutes the largest area of biotechnology research in the DOE laboratories and includes the Human Genome Project, molecular and cell biology, nuclear medicine, protein engineering, computational protein chemistry, medical informatics medical imaging and molecular toxicology. A summary of the types of projects in the three areas of biotechnology at each of the DOE laboratories is provided in Table 3. These descriptions summarize only a portion of the biologically based work at DOE facilities. More detailed summaries, which illustrate the richness and depth of biotechnology related work at some of the DOE laboratories, are included in Appendix A.

Across the areas of bioprocessing, biomedicine, and biotechnology in environmental engineering, total funding from the DOE, work for others and CRADAs is approximately $350 M in FY94. It is important to emphasize the approximate nature of this figure, for it varies with the definition of biotechnology. (In the broadest definition of biotechnology, the total value of projects could reach $450 M in FY94.) Biomedicine accounts for about 55% of the total budget, environmental biotechnology approximately 30% and bioprocessing roughly 15%. However, DOE also sponsors biotechnology research in agriculture, and supports general infrastructure improvements, such as a national X-ray synchrotron facility. These programs are not included in the $350 M budget referenced above.[5]

Approximately 50% of all biotechnology work is funded directly by DOE, with the rest coming from other federal agencies and CRADAs with industry. This figure will probably grow in inflation-adjusted dollars as DOE laboratories seek to apply their technological infrastructure to meet new requirements, such as national competitiveness and to address issues such as improved cost effectiveness in health care delivery. Further, national laboratory expertise in technology for nonproliferation, traditionally based in nuclear weapons nonproliferation is already entering into chemical weapons, nonproliferation and may also find application in biological weapons nonproliferation as well.

Outside of its national laboratories, the DOE also sponsors work in various fields of biotechnology at universities. The budget for these projects is small compared with the work at national laboratories and will not be referenced further in this report.

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[5] For a detailed review of federally sponsored biotechnology research, including programs within the DOE, see: *Biotechnology for the 21st Century - A Report by the Federal Coordinating Council for Science, Engineering, and Technology*. February 1992, U.S. Government Printing Office, Washington, D.C. ISBN No.0-16-036101-X.

Table 3. Classification of Biotechnology Programs at DOE Laboratories

Lab	Bioprocessing	Biomedicine	Environmental
ANL	Bioconversion of waste Metabolic engineering	Computational biology Cellular biology Structural Biology Genome characterization	Site characterization Modeling
BNL	Biocatalysis Fossil fuels	Nuclear Medicine Molecular/cell biology Gene sequencing Protein chemistry	Soil remediation Radioactive decontam Environmental monitoring
INEL	Fossil fuels Microbiology	Neutron capture therapy	Biosensors Subsurface microbiology
ITRI		Molecular/cell biology Human disease modeling Mechanisms of disease Immunology Cancer biology Genetic susceptibility	Biomarkers Environmental lung disease
LBL	Biomass separation	Hunan Genome Structural biology Human disease modeling Molecular/cell biology	
LLNL	Biofilters	Structural biology Genomics Bioinstrumentation Disease susceptibility	Bioremediation Dose assessment Biomarkers
LANL		Human Genome DNA repair studies Medical radioisotopes Structural Biology Magnetoencephalography Cell cycle	Bioremediation DNA forensics
ORNL	Fermentation of biomass Biomass separation	Structural biology Protein engineering Human disease modeling Mouse genome studies	Biomarkers Bioremediation Molecular ecology Plant sciences
PNL	Downstream processing	Medical informatics Medical imaging Molecular/cell biology	Microbial genetics Biogeochemistry Structural biology Subsurface microbiology
SNL		Biomedical engineering Medical imaging	
NREL	Fermentation Photobiology Metabolic engineering		Biomass CO2 fixation

Thus, from the perspective of both the DOE national laboratories and sponsoring offices with the DOE, biotechnology programs represent a significant and growing area of research and development. Because of the dual-use nature of biological processes, materials, equipment, and knowledge, a compliance monitoring regime for the BTWC may be concerned with such government sponsored programs. The DOE Office of Nonproliferation and National Security therefore requested a survey of biotechnology programs in DOE national laboratories to assess the potential impact of measures that might be part of a monitoring protocol for the BTWC. The next section of this report summarizes the design and results of that survey.

2. DOE Facilities Survey: Potential Impacts of Monitoring Measures for the Biological and Toxin Weapons Convention

2.1. Overview and Background

As the preceding text makes clear, many DOE activities may fall within the guidelines of activities that may be scrutinized by international inspectors under a potential BTWC monitoring regime. Therefore, DOE has a strong interest in understanding the implications of these potential treaty modifications for DOE facilities.

The fundamental national security objectives of the United States with respect to the Biological and Toxin Weapons Convention are to encourage universal adherence, enhance compliance, and to deter violations of the Convention. As part of the administration's review of nonproliferation policy (Presidential Decision Directive/NSC-13), the President has directed that the U.S. Government seek new measures to strengthen the BTWC. The U.S. Government will take specific steps to provide increased transparency of potential biological weapon-related activities and facilities in an effort to help deter violations of and enhance compliance with the BTWC. An Interagency Working Group (IWG) will evaluate a range of compulsory data submission and inspection measures for the BTWC that is consistent with the recently completed work of the Special Conference. The origin of some of the measures under consideration is the group of technical experts, mandated by the BTWC, to study measures from a scientific and technical standpoint. Additional measures may be considered by the IWG.

Additions to the existing confidence building measures for the BTWC could contribute to the achievement of these objectives by fostering greater openness and transparency with respect to biological activities and facilities. The U.S. Government will seek to identify cost-effective measures to be proposed to a Special Conference of the BTWC for purposes of increasing the transparency of activities consistent with the Convention. As noted above, some of these measures have their origin in the recently completed work of the BTWC ad hoc Group of Verification Experts. PPD/NSC-13 has directed that executive agencies evaluate these measures and a range of other compulsory data submission and exchange visits designed to check consistency of declarations.

The purpose of this study was to inform and notify DOE facilities of these proposed transparency measures and to request an assessment of the impact, if any, these measures will have on sensitive activities, including those of potential commercial importance that take place under cooperative research agreements with industry. Even though DOE facilities have not been and are not part of the United States biological weapons defense program, many DOE activities may fall within the guidelines of activities that may be scrutinized by international inspectors under the spectrum of potential monitoring regimes, which may emerge from the BTWC talks. Therefore, DOE has a strong interest in understanding the implications of these potential treaty modifications for DOE facilities. It must be assumed that some of these proposed measures may allow direct access to restricted areas by a multinational team. Proprietary or commercially sensitive

information as part of a CRADA could be compromised. Sensitive national security information could be revealed to hostile intelligence agencies as a result of the co-location of this work with biotechnology research, which may justify inspection scrutiny under the BTWC. A proposed regime may allow off-site access to areas and facilities associated with biological defense activities to include remote airborne and ground based sensing. Allowed on-site visits may include visual inspection of areas and facilities, sampling, identification, and review of pertinent laboratory and medical records. Finally, continuous monitoring of these sites by instruments and personnel may be agreed.

These measures under consideration by the U.S. Government are not limited to those which have been examined by the international BTWC Verification Experts Group (VEREX). While 21 off- and on-site measures have been identified and described by VEREX, others, such as the visits to declared defense related biological facilities and the investigation of unusual disease outbreaks, may be recommended by the U.S. Government during future negotiations of this proposed regime.

Thus, in the course of this study, DOE facilities with biological science projects and infrastructure were requested to assess impacts of possible verification measures in three broad categories:

- Estimates of cost for site preparation (including technology, material, manpower, and equipment requirements). In the case of more intrusive measures (such as on-site visits), costs may include lost opportunity expenses from facility shutdown if necessary to prepare for and/or carry out some of the measures such as on-site inspection. For other measures, there may be minimal, if any, site preparation costs.

- Where appropriate, estimate cost of security measures to protect against visitor activities during the execution of measures, which may be unrelated to the scope or intent of the BTWC.

- Impact on scientific research and other permitted activities and their implications for confidentiality of information. In particular, if the site is involved in work-for-others contracts that contain confidentiality agreements, an assessment of the potential for loss of this information with some measures is of great importance in estimating overall costs of implementation.

While no final U.S. Government position exists regarding the optimal number or the nature of transparency measures in an enhanced confidence building regime under the BTWC, proactive assessments must be conducted to ensure the continuation and security of sensitive programs and facilities. In addition, there is widespread appreciation for the numerous CRADAs now in existence between DOE facilities and private companies in the United States. Many of these CRADAs include specific language to protect proprietary and/or commercially sensitive information. Therefore, DOE sites were asked to quantify the effect, if any, of proposed compliance monitoring measures under the BTWC on these agreements. Indeed, DOE experience under national trial inspections for

the Chemical Weapons Convention strongly suggests that attention must be paid to protecting commercially valuable information.[6]

Due to the short time frame for gathering data for this study, a representative sample of DOE sites involved in biologically based research were selected for survey. At the suggestion of the DOE Division of Health Effects and Life Sciences Research, which provides the bulk of the direct DOE funding for biotechnology at DOE laboratories, the following sites were asked to participate in this project:

Site	Contact
Lawrence Livermore National Laboratory	Alan Casamajor
Oak Ridge National Laboratory	Jean McGinnis
Los Alamos National Laboratory	Paul Jackson
Argonne National Laboratory	Don Grube and Eli Huberman
Pacific Northwest Laboratory	Ron Walters
Lawrence Berkeley Laboratory	Aloke Chatterjee
Inhalation Toxicology Research Institute	Joe Mauderly
Brookhaven National Laboratory	Richard Setlow

Participating DOE laboratories and contractors were asked to provide a general description of their biological, biomedical, or biotechnology programs. In addition, participants were asked to evaluate proposed verification measures from the VEREX and to draft measures under consideration by the United States interagency working group. Descriptions of measures from the VEREX work was provided. We were available to answer questions, but the descriptions of the measures were not further narrowed. If ambiguities existed, participants were asked to evaluate measures over some reasonable range of frequency, intensity, and scope.

As requested by the DOE/Office of Nonproliferation and National Security, the material in the study is unclassified and thus, the survey was directed at unclassified work. Participants were asked to specify, to the best of their knowledge, the impact of measures on national security information that might be found in projects co-located with their biotechnology work. There may be many additional impacts of potential monitoring measures not covered by this study.

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[6] See, for example, *CWC Exercises at Savannah River* (videotape), Sandia National Laboratories, March 1992; U.S.A., Report on a United States National Trial Inspection, UN Conference on Disarmament, Geneva, CD/922; CD/.CW/WP.250, June 22, 1989; and U.S.A., Report on the Third United States Trail Inspection, UN Conference on Disarmament, Geneva, CD/1100; CD/CW/WP.359, July 14, 1991.

2.2. Presentation of Data

The author correlated results and carried out the following simple analysis. For each of the three impact areas (site security, site preparation, and protection of confidential information), the responses of facility participants were graded as

- Zero or very minimal impact
- Low impact (defined as a cost impact of less than 5% of existing budget or a small probability of loss of commercially valuable information which could affect the ability to obtain future contracts)
- Medium impact (defined as a cost impact of between 5 and 10% of existing budget or the potential for moderate probability of loss of commercially valuable information that could effect the ability to obtain future contracts)
- High impact (defined as a cost impact of greater than 10% or existing budget of the potential for high probability of the loss of commercially valuable information)

The independent opinions of the participants in the study were the sole basis for the data.

2.3. Analysis of Data

The current descriptions of potential measures are ambiguous and often ill-defined, and the scope of any single measure could vary depending on the undetermined specifics of implementation. As responses from surveyed experts are necessarily subjective, it is not possible to perform statistical analysis on the data. Rather, impacts as described by the participants were summarized verbally and graphically. Conclusions were drawn from the draft submissions of the participants.

No attempt was made to evaluate the *effectiveness* of any measure. Rather, the study focused on the impacts (costs, potential disruption of activities, possible loss of national security or proprietary information) of measures.

2.4. Impacts by Site

2.4.1. General Trends

Most facilities reporting to the study believed that virtually all off-site measures could be carried out with zero or low impact to their sites. In particular, reporting requirements for publications, declarations, satellite and aircraft surveillance, and off-site sampling created minimal problems for biotechnology programs at most sites. However, auditing and data on specific transfers was thought by some participating sites to have a medium impact on confidentiality of proprietary information. Comments from LBL were echoed by several other participants when they noted: "All materials would have to be screened

for commercially sensitive information. Any delays in the inspection process could jeopardize millions of dollars in CRADA ... partnerships due to foreign competition". LLNL noted: "Failure of (screening) protocols to perform as expected could lead to a loss of $1 to $5 million per year in CRADA work ... and an unknown loss (probably in excess of $10 M) to U.S. businesses from foreign competition." Further study of this issue may be indicated.

Nearly all of the on-site measures were felt by most participants to have medium to high impact on their facilities. The general area of greatest impact was in confidentiality of proprietary information, with similar, though somewhat smaller impacts in site preparation costs. Site security, as defined above, was least affected. Virtually all participating laboratories believed that there was great risk to loss of commercially sensitive information which could severely or significantly impact their programs. While participants were unable to quantify precisely the probability of loss, most laboratory experts explicitly called out the potential high losses (often in the millions of dollars per year) in programs involving industrial partners. On-site sampling appeared to present the greatest concern to participants. LLNL commented on sampling:

> "Assuming that all areas of [our program] would be subject to scrutiny, an effort would need to be made to sanitize facilities of sensitive information before the inspectors enter. Providing sensitive operations were confined to a few laboratories, only those facilities would need to be secured at a cost of about $10K per laboratory. As CRADAs become more wide-spread, the range of shut downs would spread as well, up to a possible $1M to $2M maximum impact."

On the other hand, PNL felt that sampling would present little problem. This may be due to the concentration of their biotechnology program in environmental engineering, and a biomedicine program that focuses on medical imaging rather than on protein chemistry and cellular genetics as found at other DOE sites.

There was little comment on loss of national security information, largely because the vast majority of DOE sponsored biotechnology research is unclassified. Some participants at the defense program laboratories (LANL and LLNL) pointed out that classified programs are in operation in buildings near their laboratories, or that office space is shared in buildings that include classified programs.

Finally, some participants noted that the measure "Medical Examinations" might conflict with DOE policies and procedures, rather than site specific operating procedures. Experts recommended a review of the measures by appropriate legal experts with DOE headquarters, with specific focus on "Medical Examinations."

2.4.2. Summary of Major Impacts by Site

Lawrence Livermore National Laboratory – LLNL. The LLNL Biology and Biotechnology Research Program is based on core competencies in molecular genetics, mechanisms of DNA repair, human mutation assessment, molecular toxicology, and in various technology developments deriving from this expertise. There is extensive work-for-others and a growing CRADA effort. The budget for biotechnology programs was approximately $40 M in FY94.

Off-site measures for Data on Transfers and Declarations/Notifications generate staffing requirements that may cost in excess of $100 K per year. Off-site auditing and preparation of documents for Data on Transfers could compromise sensitive information in various CRADAs. LLNL cautions that, depending on how these measures are structured, losses could amount to millions of dollars per year and/or threaten the ability of the laboratory to garner new CRADAs in the future.

On-site measures of exchange visits, interviews, visual inspections, identification of key equipment, and auditing will all require significant site preparation. However, the greatest concern is for potential loss of proprietary information from these same measures. A detailed understanding of the operational characteristics of these measures is required before precise impacts can be assessed; but costs in terms of loss of sensitive commercial information could be large (in millions of dollars). As CRADAs make up a growing part of the biotechnology effort at LLNL, site experts are concerned about protecting this information to preserve the laboratory's competitiveness.

Oak Ridge National Laboratory – ORNL. Biotechnology at ORNL derives from expertise in structural biology, determination of protein structure, mass spectrometry of large molecules, protein engineering, and recombinant DNA. A substantial portion of biotechnology efforts at ORNL are applied to environmental monitoring and remediation, with a substantial effort in bioprocessing and biocatalysis. The budget for biotechnology programs at ORNL was approximately $50 M in FY94.

ORNL experts had little concern over the impacts of most off-site measures. However, they noted that current publications, which could easily be made available to the BTWC, are sanitized carefully to remove proprietary information; therefore, preparation costs for off-site measures and impacts on confidential business information were judged to be low.

On-site measures of exchange visits, interviews, visual inspections, identification of key equipment, audits, and sampling were all thought to have the potential to compromise proprietary information of value, which could be measured in millions of dollars per year if CRADA rights are not carefully protected. Site preparation would be devoted to protecting these CRADA rights. Potential impacts would depend strongly on the details of implementation of the on-site measures.

Los Alamos National Laboratory – LANL. LANL's biotechnology program is focused largely in biomedicine, with substantial work in the Human Genome Program, molecular genetics and mechanisms of DNA repair, and structural biology. Biotechnology program funding at LANL was approximately $33 M in FY94.

As with other laboratories, off-site measures of concern to LANL experts were Data on Transfers, Multilateral Information Sharing, and Auditing. The main impacts were in protection of commercially important data. However, in addition, LANL experts were concerned about Ground-Based Surveillance and Off-Site Sampling. LANL noted: "with appropriate technology, it would be possible to identify and determine the DNA sequence

of any gene under study for proprietary or classified reasons. It is very expensive to eliminate genetic materials from laboratory effluent and this would require protection." In this vein, LANL also commented: "Effluent from laboratories conducting biological research would require collection and extensive treatment prior to release off-site. This would require capital and ongoing personnel costs."

On-site measures presented moderate and high levels of concern to LANL. Site preparation costs for on-site Auditing, Sampling, and Continuous Monitoring were thought to have the potential for high costs. In addition, these measures were seen as a threat to protection of commercially valuable information. For example, LANL noted: "it will be virtually impossible to eliminate the possibility of genetic analysis of samples with commercial or proprietary connections. Even a shutdown and thorough cleaning of the laboratory will not eliminate this. Moreover, access to stored laboratory samples will allow a complete genetic analysis of the samples using current commercially available technology. This is a serious concern."

Argonne National Laboratory – ANL. The Center for Mechanistic Biology and Biotechnology and the Environmental Research Division undertake research in biomedicine and environmental biotechnology. Core capabilities are in computational biology, structural and molecular biology, genome sequencing, bioprocessing and environmental site characterization. In addition to funding from DOE, ANL has a strong work-for-others program and evolving CRADA activities. The budget for biotechnology programs at ANL is estimated at $12 M in FY94.

Reviewers at ANL largely agreed with responses on the impacts of off-site and on-site measures. ANL pointed out that its site security is currently minimal and would have to be augmented to escort on-site visitors. ANL also noted that it was difficult to estimate specific costs of implementing measures because the current descriptions in VEREX are insufficiently detailed. However, on-site sampling was a measure of particular concern to ANL experts who noted: "First, inspectors would likely need major briefings on the types of activities going on just to decide what types of samples to collect. Second, sampling would probably require dual samples (theirs/ours) and the accompanying cost to us of having our sample analyzed. Third, if (for example) the inspectors wanted a DNA/plasmid sample, would that sample be lost to us for good? Finally, the difficulty of ensuring that any sampling/testing protocol has virtually no false positives and must be addressed. It could be a major problem and cost to undertake proof that a positive result was false."

Pacific Northwest Laboratory – PNL. Most DOE funded biology programs at PNL are conducted for the Office of Health and Environmental Research (OHER). Current programs include: molecular and cellular research, research on radon and other alpha-emitting nuclides, radiological and chemical physics of biological damage, dosimetry, structural and computational biology, large-biomolecule analytic studies and terrestrial ecology. The large work-for-other programs are the toxicology program, conducted for the National Toxicology Program and several state and private industrial clients and the Bioelectromagnetics Program, supported in part by the Electric Power Research Institute,

the Department of Defense, and the National Institutes of Health. An animal colony is maintained for toxicological research, consisting of several thousand rodents. In the past, dogs were also kept in the colony.

PNL experts believed that the costs of off-site and on-site measures to be zero or low. However, in the circumstance of shutdown of facilities to protect a client's confidential information, nominal losses could be large. Thus, PNL reviewers believed that it was important to protect proprietary information, and if shutdown could be avoided, costs would be insignificant.

Lawrence Berkeley Laboratory – LBL. LBL maintains competencies in structural and molecular biology and molecular genetics. A significant portion of their biotechnology program is directed to the field of biomedicine, and includes programs in human genome research and models for human disease. The approximate size of funding for biotechnology programs at LBL is approximately $40 M.

LBL believes that there will be costs associated with screening information made available for several off-site measures, to protect proprietary information. While LBL believes that existing publications are screened for commercially sensitive data, "some proposals contain commercially sensitive data that, if obtained by a competitor, could jeopardize both the project itself and the companies' competitive position in the market sector." Similar concerns applied for the Auditing measure. Like most other participating laboratories, LBL felt that there was virtually no impact from off-site surveillance or sampling.

Site preparation for on-site measures was a source of much concern. Laboratory programs would require careful screening to protect proprietary information, and shutdowns would be expensive. Sampling and Identification of Key Equipment were particularly sensitive in this regard.

Inhalation Toxicology Research Institute – ITRI. The Inhalation Toxicology Research Institute is a Federally Funded Research and Development Center (FFRDC) operated for the DOE by the Lovelace Biomedical and Environmental Research Institute, a non-profit subsidiary of the Lovelace Medical Foundation. Approximately 80% of the Institute's research is funded by DOE; the remainder is funded by a variety of governmental, trade association, and industry sources. ITRI's primary mission is to conduct basic and applied research into the nature and magnitude of human health impacts of inhaling airborne materials in the home, workplace, and general environment. Institute research programs have a strong basic science orientation with emphasis on the nature and behavior of airborne materials, the fundamental biology of the respiratory tract, and the mechanisms by which they cause disease. ITRI provides a national resource of specialized facilities, personnel, and education activities serving the needs of government, academia, and industry.

Programs at ITRI include Radiation Toxicology, Aerosol Science, Chemical Toxicology, Applied Toxicology, Disease Pathogenesis, and Cancer Mechanisms. Much

of the work centers around toxicity from inhaled particles and gases, but also include extensive research into immune responses in respiratory disease. Competencies includes molecular biology, biochemistry, pathology, physiology and inhalation exposure technology.[7]

ITRI experts were concerned that "the greatest risk of inspection activities would be the potential release of proprietary information generated under work for non-DOE sponsors. ... it might be assumed that our loss of ability to ensure a sponsor of the security of information related to their sponsored research might lead to a loss of an average of $1 M per year in research funds at ITRI."

Brookhaven National Laboratory – BNL. BNL conducts research focusing on protein chemistry and biomedicine. There is also work in environmental remediation.

BNL experts were not concerned about the potential for loss of proprietary information. However, there was some concern expressed over the disruption in normal laboratory routines and ongoing research. There was insufficient detail in the BNL response to provide further data for presentation or analysis.

A table of scored responses, by measure and site, is attached in Appendix B.

[7]Program description excerpted from *Annual Report of the Inhalation Toxicology Research Institute,* Prepared for U.S. Department of Energy under contract #DE-AC04-76EV01013.

3. Conclusions and Recommendations

Department of Energy Laboratories and other contractors funded by the DOE carry out a wide variety of research in fundamental aspects and applications of biotechnology. Even though DOE laboratories do not engage in research in defense against biological weapons, under the terms of a regime to enhance compliance with the BTWC, many of these programs could come under scrutiny. This survey indicates that in many circumstances, site preparation costs for on-site measures could be high. Further, and probably more important, there is widespread concern over the potential loss of commercial or business information of importance to industrial partners of these facilities.

There are several important limitations to this study. First, none of the experts who participated in the survey are experts in treaty monitoring, on-site inspections, or arms control compliance monitoring. Thus, the experts could be expected to underestimate the kinds of site preparation that might be required in response to on-site measures for treaty monitoring, including a putative BTWC regime.

Second, the experts were asked to make judgments regarding measures that are as yet often poorly defined. As several of the experts noted, estimates for possible losses or risks depend strongly on the details of implementation of measures. Experts often provided comments based on a wide range of assumptions, which could nonetheless be valuable to decision makers evaluating the benefits and risks of adopting measures to monitor the BTWC.

Third, participants were asked to limit their evaluations to unclassified programs and to impacts that directly affected their programmatic areas. There may well be additional, and significant, national security concerns if there are classified programs employing techniques common in biotechnology. There may also be impacts on national security programs that are located in or near facilities housing unclassified biological research programs should on-site inspections or other on-site measures take place.

Fourth, all of the judgments provided by participants are subjective in nature. Given the ambiguity in the description of most of the potential measures for the BTWC and the wide range of application of measures or combinations of measures, such subjectivity is inevitable. Statistical analysis of the responses is not possible. On the other hand, the observations of the site experts is useful to illustrate the possible or likely effects of certain measures on facility operations and competitiveness.

Finally, this study made no effort to analyze the potential benefits of monitoring measures for the BTWC.

Several major conclusions are evident from the data:

1. DOE laboratories possess an enormous range of expertise in biotechnology. Programmatically, DOE laboratories are involved in research and development in biomedicine, bioprocessing, environmental biotechnology and other areas of applied and fundamental biologically based research. The budget for biotechnology programs is at least $340 M per year, and is perhaps much larger when a broader definition of biotechnology is used in characterizing programs. There is a significant amount of work-for-others and CRADA supported effort, in addition to direct DOE funding.

2. Measures proposed by the ad hoc Group of Government Experts (VEREX) could result in significant impact in these programs due to the potential to intrude on contractual obligations in CRADAs to protect proprietary information. The precise nature of the impact will depend greatly on the specifics of implementing the measures. Losses can be very large as a percentage of total program budget, and may threaten the ability to garner future contracts with industry or affect laboratory competitiveness.

3. On-site measures of sampling, auditing, continuous monitoring and identification of key equipment were consistently noted to be of greatest concern to experts at DOE laboratories or sponsored sites.

4. Potential impacts vary from laboratory to laboratory, which suggests strongly that specific characteristics of research at each site determine the nature and extent of the effect of measures, particularly on-site measures. Further, the specific concerns over technical impacts of potential BTWC measures on biotechnology programs are likely to be different than the effects of CWC verification on the chemical industry. This is due to the markedly different nature of the technology, processes, and products in biotechnology efforts as compared to the chemical industry. (For example, individual bioengineered organisms or molecules represent years of research and large dollar investment. Compromise of these apparently simple entities could severely undermine competitive position.) In addition, some laboratories surveyed devoted considerably more internal effort than others in analyzing the potential impacts of the measures, which may account for some of the variation in opinion from site to site.

5. With sufficient screening of documents, DOE sites can comply with most of the requirements of off-site measures as outlined in the VEREX descriptions. However, even in the case of off-site measures, preparation of appropriate documents may be costly due to the need to remove classified, sensitive, or proprietary information.

6. For some DOE sites that currently have small or absent site security, significant expenditure may be required to escort visitors from an international organization, such as one carrying out compliance measures for the BTWC.

7. DOE sponsored laboratories other than national laboratories (such as the Inhalation Toxicology Research Institute in Albuquerque, NM) maintain highly specialized technologies, such as aerosol technology and disease pathogenesis, which will almost certainly be of relevance to the BTWC and measures under consideration to strengthen the Convention.

8. Although this study made no effort to analyze the potential benefits of monitoring measures for the Biological Weapons Convention, the high likelihood of significant adverse impact of monitoring measures on existing permitted work in DOE laboratories strongly suggests that intrusive measures should be accepted only if large benefits can be expected. Benefits that can be obtained from off-site measures are likely to exceed costs, as these costs are assessed as low or minimal.

Several recommendations follow from this study:

1. Because potential impacts vary dramatically with the details of measures under consideration for the BTWC, technical representatives from DOE laboratories and DOE sponsored biotechnology programs should be consulted as the DOE participates in the interagency process of drafting a United States position. In addition, DOE experts would be helpful in evaluating the technical benefits and limitations of specific measures to strengthen the BTWC, including new measures that may be proposed to supplement those in the VEREX work.

2. Classified programs were not considered in this study. Separate work should be considered to determine the extent of classified biotechnology-based research at DOE facilities, or sponsored by the Department.

3. A national trial inspection (NTI) at one or more DOE sites should be undertaken, which emphasizes on-site measures that may be costly to programs. The NTI should build on the lessons learned from NTIs conducted previously for the Chemical Weapons Convention, but which should be designed to emphasize the intrinsic differences between the concerns of the BTWC and the CWC. Specifically, the technical issues associated with sampling and sample analysis, the impacts on the specific confidential proprietary information in DOE biotechnology programs, and perhaps mechanisms for undermining measures could be evaluated.

4. The expertise of DOE researchers working in various fields of biotechnology may be useful resources for educating negotiators at a multinational forum. Consideration should be given to a joint industry-DOE effort to provide seminars and materials to participants in the negotiations for the BTWC.

Note added

At the time of initial drafting of this report (mid-1994), Sandia National Laboratories had limited activities in biotechnology, as indicated by budgetary allocation, compared to other DOE laboratories. For this reason, SNL was not surveyed as a part of this study. However, in the past few months (early 1995), SNL has been awarded a $4 M contract by the Army's Engineering Research Development Center for study of spectroscopic signatures of biological materials, including bacteria, viruses, and toxins. The study, known as SPECTRE (Spectroscopic Excitation and Classification of Trace Effluents), will establish a database of spectroscopic signatures and will apply unique Sandia-developed algorithms (multiwavelength ultraviolet fluorescence spectroscopy and computationally intelligent algorithms) to distinguish and classify the signatures of a defined set of biological materials. SPECTRE is unclassified, though the limitations and capabilities of the technology may be classified in the future, depending on results. It is clear that SPECTRE will be declared under the existing BTWC confidence building measures, and could be declared under any future monitoring regime for the BTWC as part of the United States Biological Defense Research Program. Should on-site monitoring activities become part of a future protocol for the BTWC, SNL will likely sustain costs of site preparation and site security similar to those of the large DOE Defense Program laboratories. In addition, as a result of the large number of Cooperative Research and Development Programs (CRADAs) at SNL, some commercial information of no relevance to the BTWC could be compromised unless efforts are undertaken to protect this data.

Appendix A

Lawrence Livermore National Laboratory
Biology and Biotechnology Research Program
Program Description

Oak Ridge National Laboratory
Biotechnology Program
Program Description

Lawrence Livermore National laboratory

Biology and Biotechnology Research Program
Program Description

Our existing core competencies are in molecular genetics and genomics, DNA repair, human mutation assessment, molecular toxicology, and technology development. They are embedded in all of our research projects. The broad scientific objectives of our program are to:

- Unravel the structure of mammalian chromosomes and the genetic code which serves as the blueprint for the body's proteins, hence, its structures and functions;
- Identify and characterize the genes that can repair damage to DNA and understand how these genes prevent or ameliorate damage;
- Develop and apply methods to assess risk to humans from exposure to radiation and chemicals;
- Develop biophysical techniques to understand protein structure and function;
- Develop and apply new instruments, procedures, and computer software to aid biotechnology research and technology transfer;
- Coordinate and develop healthcare technologies within the context of LLNL science and engineering expertise.

Molecular Genetics and Genomics. In the area of molecular genetics and genomics, our Human Genome Center has constructed a high resolution physical map of chromosome 19 in cosmids, one of the most extensive maps available to the scientific community today. We are in the process of identifying all the genes on this chromosome and sequencing selected regions. Our scientists played a key role with collaborators worldwide in identifying the structural defect in the most common form of adult muscular dystrophy - myotonic dystrophy. We are also striving to identify a number of genes associated with common diseases. Our informatics effort has demonstrated leadership in the scientific community in graphical databases for visualizing map data and for networking these data to other databases and users. The National Gene Library Project has relied on unique flow-sorting technology and molecular biology expertise to create chromosome-specific cosmid libraries for use by the scientific community. As the physical map of chromosome 19 draws to completion, we will shift some of our mapping resources to gene discovery, i.e. finding all the genes on this chromosome, and also increase our effort in DNA sequencing.

DNA Repair. Our research focuses on repair processes that correct DNA damage produced by chemical mutagens and radiation, both ionizing and ultraviolet. The pace and excitement associated with our DNA repair work has intensified in the last few years primarily because we created the resources—such as DNA repair-deficient cell lines—necessary to identify, isolate, and characterize the DNA repair genes. We have isolated, cloned, and mapped

several human repair genes associated with the nucleotide excision repair pathway and involved in the repair of DNA damage after exposure to ultraviolet light or mutagens in cooked food. We have shown that a defect in one of these repair genes, *ERCC2* , is responsible for the repair deficiency in one of the groups of patients with the recessive genetic disorder xeroderma pigmentosum (XP group D). This year, we began exploring ways to purify sufficient quantities (milligrams) of the protein products of these and other repair genes so that we can understand their functions. For example, the human *XRCC1* repair gene we isolated at LLNL is being used to purify the encoded protein from bacterial and mammalian cells so that we can determine its precise role in repairing DNA strand breaks. Our long-term goals are to link defective repair proteins to human DNA repair disorders that predispose to cancer, and to produce transgenic mice—ones that are deficient in their ability to repair DNA. Such mice can serve as models for the human repair disorders and for studying the role of repair in the origin of mutations, aging, and other processes.

Human Risk Assessment and Molecular Toxicology. We take pride in our highly interactive team dedicated to the development, validation, and application of methods to assess mutations in humans. Many of the biomarker tools have been developed at Livermore such as the automated erythrocyte glycophorin mutation assay and chromosome painting. We have applied the former to quantify mutation induced in populations exposed to acute and chronic radiation and chemical exposure. In addition, it has been used to demonstrate that individuals at high susceptibility to cancer have a higher mutation frequency at this locus. We have used the chromosome painting methods to identify chromosomal rearrangements in somatic cells and aneuploidy in sperm in normal and exposed individuals. Abnormalities in sperm directly translate into known reproductive risk. These methods are coupled to traditional methods of somatic and heritable mutation analysis also present in our program for studies on exposed human populations, e.g. the survivors of the atomic bomb and the Chernobyl accident victims. In addition, they have been useful techniques to assess genetic instability in "unexposed" people. An excellent analytical and synthetic chemistry expertise is the trademark of our molecular toxicology efforts. Using the accelerator mass spectrometer (AMS) in collaboration with the Geosciences and Environmental Research Program at Livermore, we quantify DNA adduct damage at the lowest recorded levels and link the damage to exposure and to its metabolism. We are considered one of the leading laboratories in the world in the field of dietary mutagenesis. This is a large project funded by several agencies. We have demonstrated that mutagens are formed in the cooking and processing of food. We have identified these mutagens, synthesized them in the laboratory, and applied them to studies of damage assessment in vitro and in animals. Using the accelerator mass spectrometer at Livermore we have measured levels of adducts induced in mice by feeding them mutagen at levels present in the ordinary human diet. We are expanding our AMS studies to quantify low-level exposures to benzene and other chemicals. The new AMS technology has created considerable interest in monitoring low-level exposures (one part per billion or less) in environmental samples as well as in humans.

Technology Development. The development of new technologies has always accompanied our basic and applied efforts in biomedical research. With the increased emphasis on technology transfer today, new biotechnologies are assuming even greater importance. We have now completed the development of a prototype high-speed flow cytometer and sorter and transferred to industry the information and materials necessary for its commercialization. In the genome area, we have designed and constructed a new, high-density, 384-well microtiter dish, which is also being transferred to industry. This dish allows us to store and process DNA or DNA clones at four times the unit density (384 versus 96 samples in the same area), thus reducing the storage-capacity needs and simplifying sample handling. We have recently consummated a CRADA with the Applied Biosystems Division of Perkin Elmer Corporation to develop a high-speed, high-throughput electrophoresis system for DNA sequencing. This instrument should increase rates at least tenfold for DNA sequencing and perhaps higher for other applications. As in the past, our efforts related to instrumentation make use of the expertise in the Computations and Engineering Directorates at LLNL and also rely heavily on industrial collaboration. We are beginning to explore new approaches to high throughput PCR and to the automation of DNA sequencing.

New Initiatives. We have initiated a major thrust in structural biology including protein crystallography, x-ray diffraction, high resolution NMR, and computational modeling which will examine the structure and function of our repair proteins and those proteins involved in packaging DNA in sperm. We are also beginning to exploit some spin-offs from the human genome project. One new effort involves forensic applications of DNA sequence information. The second effort involves the study of human DNA sequence variation. We have also formed a Center for Healthcare Technology at Livermore under the cognizance of the Associate Director for Biology and Biotechnology. This Center has a Working Group with a senior representative from every Directorate. The purpose is to coordinate healthcare technology efforts across the entire laboratory, to initiate new thrust areas, and to establish a credible effort that contributes to the national healthcare needs for cost-effective technologies. The Center will focus on applications in diagnosis, screening, prevention, minimally invasive medicine, and information management. The Center is looking forward to the potential new initiative in this area developing within OHER and is ready to assist DOE as needed.

Health and Ecological Assessment Division
Program Description

The mission of the Health and Ecological Assessment Division (HEA) is to perform fundamental research in the environmental sciences in support of Department of Energy (DOE) objectives. Research in HEA includes the development of methodologies and instrumentation to detect and quantify

environmental pollutants from DOE and related operations, development of models to predict transport of contaminants through multiple environmental media (e.g., air, water, ground, biosphere), development of dosimetry capabilities for radiation and chemicals, and the development of expertise in risk assessment. In addition to research and development (R&D) activities in these areas, HEA scientists apply their expertise to help solve difficult DOE, national, and state environmental problems.

HEA consists of five interrelated environmental research groups, as well as a center that compiles, integrates, interprets, and translates the results of the basic and applied research conducted by these groups and other organizations, along with empirical data, into terms that are used for assessing and explaining ecological and human health risk associated with the contamination of environmental media. The titles of these research groups and the center are (1) Ecological Response and Restoration; (2) Environmental Characterization and Integrated Assessment; (3) Exposure Assessment; (4) Dosimetry and Dose Response; (5) Measurement Science; and (6) The Risk Sciences Center (RSC). The specific objectives of each research group are described next.

The Ecological Response and Restoration Group develops and applies methods for characterizing contaminated sites, assessing ecological impacts, and supporting environmental restoration and remediation activities. The goals of the Environmental Characterization and Integrated Assessment Group are to characterize chemical and radioactive substances in environmental media, determine contaminant transport and uptake, calculate doses to exposed populations, and evaluate and recommend remedial measures that reduce the severity of potential impacts. The Exposure Assessment focuses on creating and/or improving methods for estimating human exposures to radioactive and nonradioactive substances in environmental media for the purpose of strengthening health-effects risk assessments of emerging energy technologies and associated with the cleanup of hazardous-waste sites. The Dosimetry and Dose-Response Group concentrates on providing technologies and methods for use in monitoring, detecting, or modeling the relationship between exposure to environmental contamination (e.g., chemical or radiological) and health effects. The Measurement Sciences Group develops and explores the applications of optical spectroscopy and chemical-specific sensors for the real-time detection and monitoring of chemical compounds in media associated with the environment and/or an engineering process. The principal research of the RSC is directed toward providing realistic analyses of human-health and ecological risk resulting from existing situations, emerging technologies, or the adoption of specific policies. All of the research being conducted by these groups and the RSC support the activities of the U.S. Department of Energy, the nation, or the states.

Description of Biotechnology Program at Oak Ridge National Laboratory

Biotechnology at Oak Ridge National Laboratory (ORNL) is a cross-cutting activity involving numerous research divisions. At ORNL, biotechnology research is conducted at various stages of biological organization, ranging from molecular through organismic and system levels, and addresses basic and applied research questions as well as bioprocessing development and appropriate socio-economic issues. The following discussion covers existing and proposed investigations in all of these areas.

Structural biology activities incorporate experimental techniques that derive three-dimensional structural information from the analysis of radiation in various segments of the electromagnetic spectrum that are scattered by biological materials. Paramount among scattering techniques in structural biology are X-ray and neutron small-angle scattering, crystallography, and several forms of biological imaging. Protein engineering is another important experimental tool in structural biology. Bioprocessing capability and areas of computational biology support the scattering methods. ORNL strengths in all of these areas are combined to address structural biology problems.

Proteins being studied for three-dimensional structure determination include phosphoribulokinase, human epidermal growth factor (EGF), and mutant analogs designed by ORNL's Protein Engineering Program, as well as human and mouse DNA repair proteins that remove alkylation lesions. Crystallographic studies of nucleosomes reconstituted from a cloned palindrome DNA restriction fragment are underway.

Mass spectrometry is becoming an increasingly important tool in structural biology; it has broad applications ranging from large biopolymer sequencing to the unambiguous identification and structural characterization of trace biomolecules. Among the unique capabilities at ORNL are trapped ion techniques, including Fourier transform ion cyclotron resonance mass spectrometry (FTMS) and quadrupole ion trap mass spectrometry, which have unique capabilities for probing the structure of trapped ions generated from biomolecules. In addition, a number of other types of mass analyzers and ionization techniques are being employed for the analysis of biomolecules with masses exceeding 100,000 Daltons. The ability to image biological materials with mass spectrometry has also been developed in the Chemical and Analytical Sciences Division. This tool has wide-ranging applicability for detecting specific molecules in target organs, for example. Laser mass spectrometry for DNA segments analysis, which was developed in the ORNL Health Sciences Research Division (HSRD), has proved to be a valuable tool for determination of the structure of DNA and protein. It should play a more important role for structural biology research in the future. HSRD is working to develop laser-based optical spectroscopies for determining the structural characteristics of biological molecules. These spectroscopies are based on the measurement of chiroptical effects, which provide details about the spatial configurations of the constituent functional groups of chiral molecules. Biological imaging makes use of expertise concentrated in HSRD and involves a novel class of microscopes that have been identified as a cost-effective, high-volume technique for studying DNA. Techniques used in these studies include atomic force microscope (AFM),

studied to help understand the microscopic form-function relationships and to perform rapid high-resolution mapping. Hybrid instrument techniques combining optical and force probes are being developed to follow the dynamics of the receptors on living membranes.

Protein engineering is an active program in the ORNL Biology Division and integrates many activities in molecular genetics. The ability to program specific mutations into cloned genes permits the systematic design of new gene products as mechanistic probes of protein function and the tailoring of operons to alter the regulation of gene expression. X-ray and neutron structural analysis of crystallizable proteins and subsequent molecular modeling with three-dimensional computer graphics will guide the selection of mutant gene products to be constructed and will serve as a tool for predicting the probable structural consequences. Because protein engineering provides an avenue for optimizing functional properties of enzymes, it overlaps with other elements of biotechnology. Computational biology involves the use of advanced computing devices and techniques for gathering and processing information on biological structures. It includes molecular visualization, rapid processing of macromolecular scattering data, prediction of molecular structure, and simulation of macromolecule behavior after chemical modification or changes in environmental influences. As such, this part of the biotechnology initiative involves a number of ORNL divisions, including Biology, Chemical and Analytical Sciences, Health Sciences Research, and Engineering Physics and Mathematics.

Substantial research in biotechnology pertaining to cellular studies at ORNL derives from considerable expertise in cloning recombinant DNA, designing hybridoma cells, studying microbial ecology, and constructing transgenic mice. Cloning, in conjunction with manipulation of cells *in vitro*, has ushered in the modern era of protein engineering, with applications in medicine, agriculture, waste reduction, and bioprocessing. Monoclonal antibodies, elicited by hybridoma cells, have wide-ranging applications, including the detection of physiological and xenobiotic molecules; they can also be used for the early detection and treatment of cancer. Transgenic mice, constructed by insertional or targeted mutagenesis, provide a means for developing experimental models for human diseases and potentially for mitigating genetic disorders by gene therapy. The modification of plants for better feed and fuel and for the enhanced production of chemicals is another important area.

Changes in DNA are the most fundamental of the effects of mutagens and carcinogens. Several approaches to detect such changes are components of the ORNL biotechnology program. The classical DNA labels, radioisotopes and fluorescence, are being supplemented with stable isotopes to provide new, rapid avenues to detecting alteration in DNA by resonance ionization spectroscopy. Characterization of a single DNA molecule is becoming feasible as a result of recent improvements in scanning probe microscopy methods, in which the probe

measures electron tunneling or atomic force on the DNA surface. Also at the molecular level, a DNA matrix that is being developed will use the basic hybridization specificity of one DNA to another to detect sequence changes that lead to mutations and cancer.

Laser-induced surface-enhanced Raman techniques are used to provide vibrational and structural information on DNA, nucleotides, and proteins. Biological markers are valuable tools for investigating recovery of ecological systems following restoration and for evaluating exposure potential to released components. Development of useful biological markers involves interdisciplinary research spanning areas from molecular biology to analytical techniques. The application of biological markers to human exposures or disease states requires the development of novel, ultrasensitive analytical techniques. DNA adducts in fish and mammals have been used to determine exposure of organisms to polyaromatic hydrocarbons. Elevated levels of mixed-function oxidase have been used to evaluate direct toxic effects, and the return of sensitive species to habitat has provided direct evidence of the success of restoration activities. New structural techniques are being devised for use with FTMS to characterize biopolymers, such as DNA, which have been modified as the result of exposure to chemicals or radiation. Advanced instrumentation based on ion trap mass spectrometers is being developed for the rapid detection of trace organics in a variety of biological and environmental matrices; thus, it has significant potential for biotechnology applications.

Bioprocessing research and development at ORNL addresses advanced processing concepts and systems that can be used for energy production and conservation, conversion of renewable feedstocks to fuels and chemicals, processing of fossil fuels, treatment of hazardous or radioactive wastes, and solving other national problems. Recent advances include the use of chemically modified enzymes to enhance the conversion of coal to liquids, new techniques for the conversion of renewable feed materials to commodity chemicals, advanced bioreactor concepts that enhance productivity by a factor of four or more, and use of bioadsorbents for the cleanup of wastewater. Cooperative research efforts being developed with industry include advanced bioreactors for the chemical industry, bioremoval of uranium from mine wastes, bioconversion of coal, and removal of sulfur from petroleum by advanced bioprocessing techniques.

Environmental biotechnology includes research in biomonitoring, biological markers, eco-toxicology, environmental chemistry, plant genetics, and microbial ecology. Efforts range from the subcellular level to the ecosystem and are directed at understanding how chemicals cause responses in biological systems and how biological systems enhance degradation and/or immobilization of contaminants in soils and groundwater. Environmental biotechnology research provides opportunities for application to environmental restoration and bio-remediation and the genetic engineering of high plants for use as producers of alternative fuels or other valuable chemicals.

Applied biological research is carried out in support of bioprocessing concepts with an emphasis on photobiology, enzymology, and microbiology. Engineering research stresses advanced bioreactor concepts, enhanced biocatalyst systems, separation technology for product recovery and purification, and system monitoring and control. Development of technology for site

remediation is also an important component of this research area. Efforts have included development of sensing devices based on fiber optics for detection of bacterial metabolism associated with degradation of wastes and monoclonal antibodies immobilized on optical fibers to provide remote sensing of hazardous chemicals in groundwater and in subsurface soil samples. Related studies use the bacteria found in association with free-living amoebae in the degradation of toxic wastes. These unique amoebae/bacterial consortia have demonstrated the ability to degrade or alter trichloroethylene and a variety of explosives.

The modification of plants for the enhanced production and isolation of valuable compounds is an important research activity, coupling plant physiology with molecular biology. Enhanced production of cellulose in biomass feedstocks is a model system, where genetic transformation techniques are being applied to amplify endogenous indoleacetic acid concentrations in hybrid poplars, altering primary carbon metabolism to increase cellulose deposition. Such studies are providing a greater understanding of basic plant metabolism that is being used to elucidate biochemical mechanisms of tolerance to environmental stress. For example, accumulation of solutes, which confer water stress tolerance in hybrid poplar, is being evaluated as a molecular/subcellular indicator of stress tolerance in plant tissue culture systems. Future research into natural plant products may yield novel bioactive compounds that can be mass produced in bioreactors containing plant cell suspension culture, using protocols derived from the model system.

Another effort in biotechnology combines those components of fundamental research which are related to the responses of environmental species with applied microbiology, engineering capabilities, and chemical detection and sensing to address environmental restoration and waste management issues.

Appendix B

- **Impact on Confidential and Proprietary Information**
- **Site Preparation Costs**

Impact on Confidential and Proprietary Information

	LLNL	ORNL	LANL	ANL	PNL	LBL	ITRI	BNL	USCF
1. Surveillance of Publications									
2. Surveillance of Legislation									
3. Data on Transfers/Production	••	••	••	••		••			
4. Multilateral Information Sharing	••		••	••	•				
5. Exchange Visits (Off-Site)									
6. Declarations			•						
7. Suveillance by Satellite									
8. Surveillance by Aircraft									
9. Ground Based Surveillance			•						
10. Sampling and Identification (Off-Site)			•						
11. Observation (Off-Site)									
12. Auditing (Off-Site)	••	••	••	••		••			
13. Exchange visits	••	••	•	••		•	••		
14. Interviewing	••	••	•	••	•	••	••		
15. Visual Inspections	••	••	•••	••		••/•••	••		
16. Identification of key equipment	••	••		••		••/•••	••		
17. Auditing	••	••	••	••	•	••/•••	••		
18. Sampling and Identification	•••	••	•••	•••		••/•••			
19. Medical Examination					•				
20. Continuous Monitoring by Instruments	••	••	•	••					
21. Continuous Monitoring by Personnel		••	•••						

Key: No mark = No impact
- • = Low or minimal impact
- •• = Medium impact
- ••• = High impact

Site Preparation Costs

	LLNL	ORNL	LANL	ANL	PNL	LBL	ITRI	BNL	USCF
1. Surveillance of Publications						•			
2. Surveillance of Legislation									
3. Data on Transfers/Production	•	•	•	•		•			
4. Multilateral Information Sharing			•			•			
5. Exchange Visits (Off-Site)	•	•	•	•		•			
6. Declarations	••	•				•			
7. Suveillance by Satellite									
8. Surveillance by Aircraft									
9. Ground Based Surveillance			••						
10. Sampling and Identification (Off-Site)			••						
11. Observation (Off-Site)									
12. Auditing (Off-Site)	•	•	••	•		•			
13. Exchange visits	•	••	••	•		•	•		
14. Interviewing	•	•	••	•		•	•		
15. Visual Inspections	•	•	••	•••	•	••/•••	•		
16. Identification of key equipment	•	•	•	•	•	•/••	•		
17. Auditing	••	•	••	••		••	•		
18. Sampling and Identification	•••	••	•••	•••		•••			
19. Medical Examination	••	••	••	••	•	•••			
20. Continuous Monitoring by Instruments	•••	••	••	•••					
21. Continuous Monitoring by Personnel		••	•••		•				

Key: No mark = No impact
- • = Low or minimal impact
- •• = Medium impact
- ••• = High impact

Site Security Costs

	LLNL	ORNL	LANL	ANL	PNL	LBL	ITRI	BNL	USCF
1. Surveillance of Publications									
2. Surveillance of Legislation									
3. Data on Transfers/Production									
4. Multilateral Information Sharing			•						
5. Exchange Visits (Off-Site)									
6. Declarations									
7. Suveillance by Satellite									
8. Surveillance by Aircraft									
9. Ground Based Surveillance			••						
10. Sampling and Identification (Off-Site)			••						
11. Observation (Off-Site)									
12. Auditing (Off-Site)									
13. Exchange visits			•	•			•		
14. Interviewing			•	•			•		
15. Visual Inspections			••		•	•	•		
16. Identification of key equipment			•		•	•	•		
17. Auditing			••				•		
18. Sampling and Identification	••		•••	••		••			
19. Medical Examination	••		•	••					
20. Continuous Monitoring by Instruments		•	•	••					
21. Continuous Monitoring by Personnel			N/A	••	•				

Key: No mark = No impact
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