ENVIRONMENTAL HAZARDS ASSESSMENT PROGRAM
QUARTERLY REPORT
January - March, 1994

FOR

GRANT DE-FG01-92EW50625

SUBMITTED TO THE
U. S. DEPARTMENT OF ENERGY

BY THE

MEDICAL UNIVERSITY OF SOUTH CAROLINA

May 4, 1994

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1.0 INTRODUCTION

On June 23, 1992, the U. S. Department of Energy (DOE) signed Assistance Instrument Number DE-FG01-92EW50625 with the Medical University of South Carolina (MUSC) to support the Environmental Hazards Assessment Program (EHAP).

Dr. James B. Edwards, President of the Medical University of South Carolina recently suggested that "Good Health is not the result of 'good doctorin' but the result of a healthy society in a healthy, economic, political and biological environment." In pursuit of that lofty goal he was reminded by Dr. William J. Schull, from the University of Texas Health Science Center of an old quote by Thomas Jefferson.

> "I know no safe depository of the ultimate powers of society but the people themselves; and if we think them not enlightened enough to exercise their control with a wholesome discretion, the remedy is not to take it from them, but to inform their discretion."
>
> *- Thomas Jefferson*

It is fitting that a grant of this magnitude turns to the people themselves, at the crossroads, to seek the answers. Inform their discretion. Solve problems. Move ahead.

Grant Objectives

The objectives of the EHAP program stated in the proposal to DOE are to:

1. Develop a holistic, national basis for risk assessment, risk management, and risk communication which recognizes the direct impact of environmental hazards on the health and well-being of all,

2. Develop a pool of talented scientists and experts in cleanup activities, especially in human health aspects, and

3. Identify needs and develop programs addressing the critical shortage of well-educated, highly-skilled technical and scientific personnel to address the health oriented aspects of environmental restoration and waste management.

This report describes activities and reports on progress for the third quarter (January - March, 1994) of the second year of the grant. It reports progress against these grant objectives and the Program Implementation Plan published at the end of the first year of the grant. Questions, comments, or requests for further information concerning the activities under this grant can be forwarded to Jack Davis in the EHAP office of the Medical University of South Carolina, (803) 792-1666.

2.0 PROGRAM OVERVIEW

2.1 Program Elements

To better accomplish the objectives over the years, we have organized the grant efforts into three major elements:

- The Crossroads of Humanity Series,
- Research, Science and Education Programs, and
- Program Management.

The relationship of these elements among each other is shown in Figure 2.0. Each element has a specific programmatic function which is briefly described in the following paragraphs and described in more detail in the following sections. In addition to the function, each element has the responsibility to involve people from outside MUSC faculty, staff, and students. The principal outside participants are also shown in Figure 2.0.

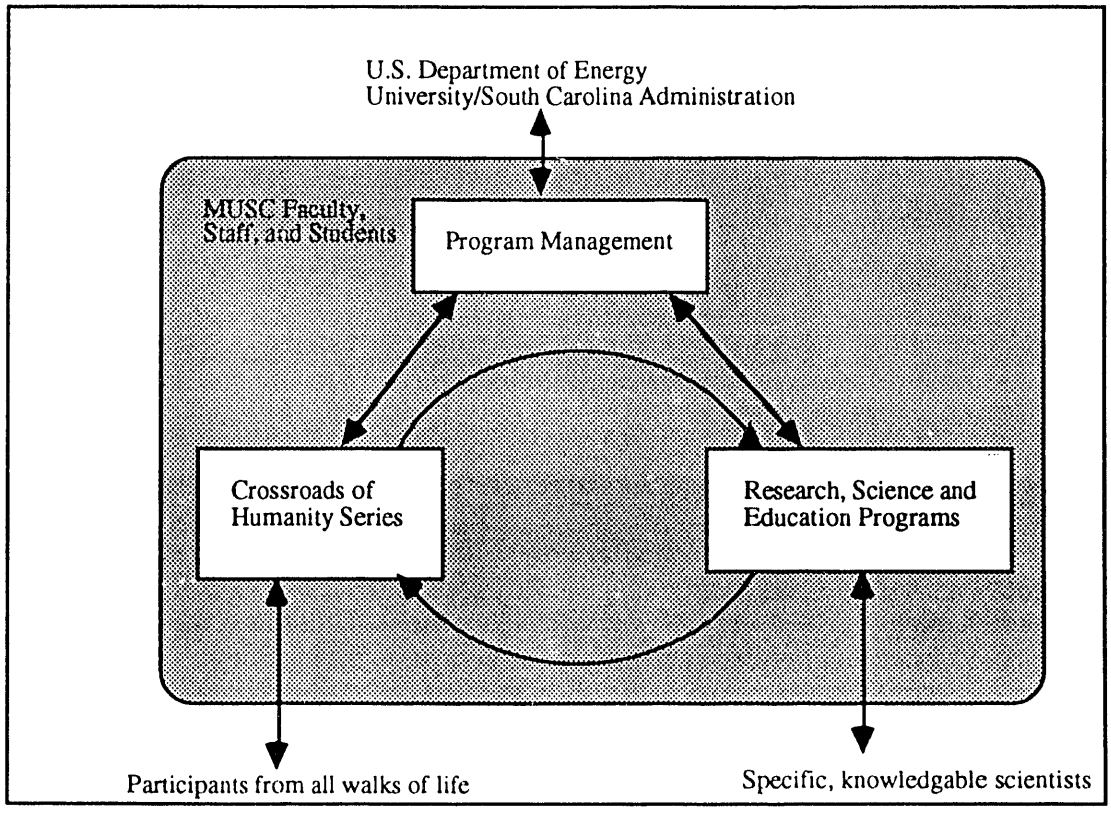


Figure 2.0. The Major Program Elements and Their Relationships.

The Crossroads of Humanity Series,with its associated projects, brings talented scientists and experts from all walks of life together to develop a new, holistic basis for risk management, risk assessment, and risk communication. That basis is focused on human health. As such, the Crossroads Series program becomes the driver for the entire grant efforts, as well as one of the places where research results are presented and used for the

public good. It is also through the Crossroads Series that we initially involve health care professionals and generate useful materials for science and education.

The Research, Science and Education Programs provide a foundation to enable health care providers and researchers to explore deeply into environmental health issues. Medical and graduate students learn about environmental health issues through research, lectures, and case studies. Faculty engage in environmental health issues through research and teaching. The science and education programs will evolve throughout the grant from programs focused on science and education objectives alone to programs focused on resolving the problems raised through the Crossroads of Humanity Series by people from all walks of life as problems needing resolution to move to a better basis for making decisions on environmental cleanup.

The Program Management element provides reporting, budgeting, and accounting as well as monitoring and program direction to those actively involved EHAP initiatives to ensure we accomplish the grant objectives in an effective and efficient manner. The Program Management group is also primarily responsible for developing ties with other universities and research laboratories to ensure we are working cooperatively with other researchers engaged in closely related issues and projects.

2.2 Program Expenditures

The following presents an overview of the Third Quarter Year 2 and Year to Date (YTD) grant expenditures.

EHAP 3rd Quarter Year 2 Expenditure Summary	3rd Qtr	YTD
	(Dollars in Thousands)	
Program Management	115	420
Developing Program Strategies and Plans		
Coordinating with other Institutions		
Directing and Reporting		
Crossroads Series	29	1,006
Round Tables and Workshops		
Publications and Outreach		
Expert Support		
Research and Evaluation		
Research, Science & Education	375	1,204
Toxicology		
Risk Assessment		
Information Support		
Education and Training		
Indirect Costs	229	1,129
Equipment	108	136
Total	853	3,894

Current encumbrances for salaries and purchases through the third quarter are $2,105, bringing total YTD expenditures and encumbrances to $5,999 or 86% of the approved award for Year 2.

3.0 PROGRAM MANAGEMENT

The Environmental Hazards Assessment Program Office (Program Office) was established by the MUSC administration to ensure the management of grant efforts to meet the program goals and objectives. The Program Office responsibilities include: development and implementation of the program plan for the DOE grant, development and implementation of major support systems necessary for managing and reporting on all EHAP program efforts, developing partnerships for the execution of programs with other universities and research institutions, and the development of joint venture funding of environmental programs.

The Program Office reports to the office of the Vice President for Academic Affairs and Provost. To support this office, MUSC has made non-federal funds available to the Director.

Director:	R. Martin Jones, Ph.D.
Ass't. to Director for Operations:	Jack Davis, M.S.
Ass't to Director for Univ. Programs:	Allen Smith, DR., P.H.
Ass't. to the Director for External Programs:	Robert Draughn, D.SC.
Ass't to the Director for Finance:	Susan Legare
Directc for Crossroads:	Glenn Fleming, Ed.D.
Director for Research, Science, & Education	Rosalie Crouch, Ph.D.
Administrative Assistant:	Susan Harris
Administrative Specialist:	Mimi Gainey
Administrative Specialist:	Anita Noisette
Business Manager	Gail Brubaker
Assistant Project Administrator	Marion Watson

Milestones Achieved in Third Quarter, Year 2

The Grant Principal Investigator and the Director of EHAP announced that Dr. Frank Parker agreed to serve as Chairman of the External Advisory Group (EAG) which will review all grant activities and plans and provide guidance to the Director. Dr. Parker, Distinguished Professor of Environmental and Water Resources Engineering at Vanderbilt University, is also a Westinghouse Distinguished Scientist and professor of environmental systems engineering at Clemson University in South Carolina. Prior to joining Vanderbilt, Dr. Parker was chief of the radioactive-waste disposal research unit at Oak Ridge National Laboratory from 1956-1967. He is a member of the National Academy of Engineering. His specialty is radioactive and hazardous chemical waste management.

Subsequent to signing the Memorandum of Understanding (MOU) between MUSC and the Idaho National Engineering Laboratory (INEL) in the second quarter, efforts in the third quarter focused on developing formal collaborative programs in the areas of risk assessment and risk communication. A seven-member team of scientists and researchers from MUSC headed by Dr. Rosalie K. Crouch, Dean of Graduate Studies, visited INEL to advance this process. Further preliminary discussions were held between personnel at INEL and Dr. David Hoel, Chairman of Biometry and Epidemiology, to formulate risk assessment initiatives particularly in the area of bioremediation.

Progress towards establishing a collaborative relationship between MUSC and Brookhaven National Laboratory (BNL) was continued in the third quarter when an executive team headed by Dr. James B. Edwards, President of the Medical University, visited BNL to explore areas of mutual interest and cooperation.

The third year application for continuation was completed in the third quarter. During Year 3, the emphasis in our Crossroads Series of workshops will move from the hypothetical to the actual. We begin this change in focus the next quarter with the April Crossroads of Humanity Series Program, Planning for Purity - A Community Meeting on Environmental Preparedness. Our Science and Research initiatives will continue to explore environmental health issues with some change in emphasis based on this year's results and accomplishments.

One of the changes in emphasis will be to focus on environmental medicine in the development of a more credible method for establishing "health risk" associated with environmental hazards. To that end, Dr. Allen Smith and Dr. Stanley Schuman have taken preliminary initiatives in designing, implementing and evaluating a statewide approach to preparing phyusicians for their leadership role in environmental health issues through statewide family medicine training systems and the MUSC Agromedicine program. They completed a video tape series entitled "Environmental Health for Physicians".

Dr. Smith secured a faculty appointment for Dr. Allen Ducatman as an Adjunct Professor of Medicine at MUSC. Dr. Ducatman is a highly regarded clinician in environmental medicine at the University of West Virginia. Dr. Ducatman will be instrumental in working with Dr. Smith and Dr. Schuman in developing new research initiatives combining traditional risk assessment with clinical methodologies to assess environmental hazards from a health perspective.

Milestones Planned for Fourth Quarter

The Grant Principal Investigator, the Director of EHAP and Dr. Frank Parker, newly-named Chairman of the External Advisory Group, will be working to identify and secure the services of committee members for the EAG. The process is expected to be completed by the end of the fourth quarter at which time the initial meeting of the Group will be announced.

The subcontract between MUSC and the University of Charleston for the project "Development and Implementation of a Joint Master's Degree Program in Environmental Studies" as approved by the South Carolina Council on Higher Education will be executed. The work, which covers a four-year period, will be partially funded by EHAP. The contract is subject to annual renewal only by mutual agreement of the parties upon written notification. The first year funding has been approved at $240,000 and will be expended in the fourth quarter upon completion of performance for Year 1. The Masters Program will be offered for the first time in the Fall of 1994.

The collaborative initiative with INEL will continue when a group of scientists and managers from INEL visit Dr. Hoel and his staff in April. The purpose of the visit will be to continue the development of collaborative programs in the risk assessment area. A second research cooperative program will be initiated with the visit of INEL's manager of

Buried Waste Integrated Demonstration (BWID) to the April Community Meeting on Environmental Preparedness with the purpose of modeling similar BWID community meetings after those developed in our Crossroads of Humanity Series.

In the fourth quarter, we expect to establish direct contacts with key personnel at BNL and move closer to establishing an MOU similar to that between MUSC and INEL.

4.0 CROSSROADS OF HUMANITY SERIES

Director:	Glenn Fleming, Ed.D.
Research Director:	Catherine Musham, Ph.D.
Publications Designer and Editor:	Cathi Bare
Administrative Assistant:	Percilla Coaxum
Research Associate:	Dylan Holmes
Program Information Coordinator:	Richard Jablonski
Public Information Specialist:	Todd Phillips
Events Coordinator:	Sylvia Rivers

During the Third Quarter of Year Two (January 1 through March 31, 1994), the Crossroads of Humanity Series charted a new course, incorporating "lessons learned" during previous quarters into a series of programs designed to address environmental issues in a "real world" setting.

Background
During the preceding three quarters (April 1 though December 31, 1993), Crossroads Series staff conceived, implemented, developed and studied a series of six environment-related forums and workshops. These programs presented and examined issues arising from the hypothetical "Purity scenario," in which a mythical town and its citizens face their own environmental crisis. In the process, we advanced (and continue to advance) in five areas:

- Development of a pool of talented scientists and experts in cleanup activities;
- Production of videotaped dialogues and seminars suitable for use in environment-related curricula;
- Creation of a model scenario useful to government and citizens, particularly at the local level, when they face environmental-cleanup situations;
- Generation of a list of products and services EHAP may offer in the future; and
- Direction for future issue-specific workshops and forums.

Currently
With the completion of the first six programs, EHAP staff embarked on a rigorous planning period, soliciting and analyzing in-house and external suggestions regarding future direction of the Crossroads Series.

With the hypothetical Purity scenario at a logical end point, Crossroads organizers began the transition -- as planned -- to a series of issue specific workshops and forums. These include the first meeting of EHAP's **Perceived Risk Advisory Committee** (Feb. 24-26, 1994), the first **International Conference on Immunogenetic Risk Assessment in Human Disease** (March 6-8, 1994), and **Planning for Purity: A Community Meeting on Environmental Preparedness** (April 22-23, 1994).

During the current quarter, MUSC, EHAP and South Carolina Educational Television (SCETV) reached an agreement whereby SCETV will present Crossroads Series programming on affiliates across the state. The broadcast schedule follows:

- 4/8/94, 9 p.m., In Search of Purity
- 4/15/94, 9 p.m., Purity Revisited
- 5/6/94, 9 p.m., Planning for Purity: A Community Meeting on Environmental Preparedness

SCETV marketing personnel have promoted the availability of Crossroads Series programming to television stations across the United States. Satellite transmission enables other stations to record the three Crossroads Series programs for future broadcast. Initial feedback on broadcast dates and times outside of South Carolina is promising.

Ongoing
Because, the Crossroads Series incorporates elements of research, public information, communication, expert recruitment and support of EHAP activities in areas of Program Management and Science and Education, staff devoted a portion of Year Two, Third Quarter efforts to:

- Research projects and surveys related to risk perception and risk communication;
- Publication and circulation of *EHAP News & Information*;
- Design and publication of such Science and Education-related materials as program brochures, posters and mailers;
- Development of a database including 300 experts in cleanup-related activities; and
- Identification and recruitment of those experts.

Milestones and Deliverables from Third Quarter, Year 2

4.1. Research and Evaluation

1. Completed national surveys of three groups of medical educators: academic deans, family medicine residency program directors and nurse practitioner deans. Response rates were high. Data has been analyzed and reports are being prepared for publication in scientific journals.
   - Preliminary Results to Family Practice Patient Environmental Risk Perception Survey
2. Submitted abstract on the results of the medical educator survey accepted for presentation at the **First International Symposium on Ecosystem, Health and Medicine** in Ottawa, Canada.
3. Applied for symposium entitled **Environmental Health Education in Medical Schools,** at the **Association of American Medical Colleges'** annual conference in September, 1994 (Catherine Musham, Ph.D., moderator).
4. Attended seminar entitled **Concepts of Risk Analysis,** Feb 1-2, 1994, in Charleston, SC.
5. Attended conference entitled **Health Research and the Need to Ensure Environmental Justice,** Feb. 10-12, in Washington, DC. As a result, developed an idea for an environmental equity research program in Charleston, SC.
6. Attended EHAP's **Perceived Risk Advisory Committee** Meeting, Feb. 24-26, 1994, in Charleston, SC. Committee meeting co-chaired by John Dunbar, M.D., M.P.H., and Daniel Lackland, Ph.D. Planned collaboration on Savannah River Site and other studies.
7. Research assistant Dylan Holmes provided technical assistance for the **Perceived Risk Advisory Committee** meeting, Feb. 24-25, 1994, and the **International**

Conference on Immunogenetic Risk Assessment in Human Disease, March 6-8, 1994, in Charleston, SC.

8. Attended monthly meetings of the **South Carolina Family Practice Research Consortium** to obtain support for environmental risk perception and communication research.
9. Met with Dr. David McCallum, Principal of Focus Group, to discuss our mutual interest in his serving as a consultant to the Crossroads Series Outreach Division's research program.

4.2 Workshops and Forums

1. EHAP sponsored and Crossroads Series personnel organized and assisted in execution of the first **Risk Perception Advisory Committee,** Feb. 24-25, 1994, in Charleston. Co-chaired by Daniel Lackland, Ph.D., and John Dunbar, M.D., M.P.H., both of MUSC and EHAP, the advisory committee includes nine members from various organizations and institutions worldwide.
   The eight committee members who attended the February meeting discussed a variety of issues, including the practicality and means of incorporating elements of risk perception, epidemiology and basic science into a program capable of identifying "public-acceptable" levels of environmental risk.
   - Perceived Risk Advisory Committee Meeting Notebook
   - Perceived Risk Advisory Committee Report (draft, subject to committee member approval)
2. EHAP co-sponsored and Crossroads Series personnel organized and assisted in execution of the first **International Conference on Immunogenetic Risk Assessment in Human Disease,** March 6-8, 1994, in Charleston. Co-chaired by Janardan P. Pandey, Ph.D., and David G. Hoel, Ph.D., both of MUSC and EHAP, conference speakers included 15 experts on current research efforts in the field of immunogenetics, specifically the relationship between Human Leukocyte Antigen and Immunoglobulin Genetics.
   - International Conference application brochure
   - International Conference Notebook
   - International Conference notes (pending approval)
3. Prepared for **Planning for Purity: A Community Meeting on Environmental Preparedness,** April 22-23, 1994, in Charleston. The Community Meeting will include nine panelists, all from the state of South Carolina, each representing a specific group or interest fundamental to resolution of environmental crises such as the one that struck the mythical town of Purity. WCSC-TV Channel 5 news anchor Debi Chard will moderate the program. South Carolina Educational Television will videotape the program for broadcast purposes.
4. Planning and co-sponsoring **Clues to Unraveling the Association Between Illness and Environmental Exposure,** June 3, 1994, in Charleston, SC. This workshop is designed for nurses working in community, occupational, primary care and other health care settings. Co-sponsors include the Agency for Toxic Substances and Disease Registry (ATSDR) and the South Carolina Department of Health and Environmental Control (DHEC).
   - Clues to Unraveling ... program and registration form
5. Planning and co-sponsoring The Quiet Revolution: New Grassroots Coalitions in Natural Resource Decision-Making, May 25-26, 1994, in Denver, CO.

Crossroads Series Director Glenn Fleming will serve as keynote speaker for the meeting, co-sponsored by the Center for the New West.

6. Continued planning for the Crossroads of Humanity Series International Symposium, scheduled to take place in 1995.

4.3 Publications/Information

1. Published printed materials related to Crossroads Series events in February and March of 1994.
2. Planned materials related to Planning for Purity: A Community Meeting on Environmental Preparedness. Materials to include a program brochure, posters, advertising materials and additional information sheets as needed. (3/94)
3. Published and mailed *EHAP News & Information*, a four-page newsletter to inform readers of the Environmental Hazards Assessment Program's existence, plans, goals and accomplishments. Mail circulation: approximately 1,200.
   - January-February *EHAP News & Information* (1/94)

   Next newsletter publication date: 4/30/94. Future newsletters will incorporate *Crossroads Update* as part of a revised/expanded format.
4. Developed a **Purity Case Study,** a pending publication based in large part on the Purity scenario developed during the first six Crossroads Series events. Book will contain a brief case study of the Town of Purity, followed by articles authored by Crossroads Series participants, each of whom will apply his/her expertise in environmental issues to the case study. (1-3/94)
5. Published brochure for MUSC/UoC masters program in Environmental Sciences. (2/94)
6. Published student recruitment poster for doctoral program in Environmental Risk Assessment. (2/94).

4.4 Expert Support

1. Continued Crossroads of Humanity Series of forums and workshops. Approximately 85 experts in environment-related fields participated in the first six Crossroads Series events, and over 400 citizens attended the two Crossroads Series Round Table Forums.

   As of April 6, 1994, nine panelists and a moderator have agreed to serve on the upcoming Community Meeting program. Approximately 160 citizens have requested tickets -- a pace slightly ahead of ticket demand for the previous two round table forums.
2. Continued overhaul of Crossroads of Humanity database, adding experts as they are identified/recruited and deleting those experts who have expressed no interest in EHAP (1-3/94).
3. Planned transition of Crossroads Series database to new program, enabling more efficient storage and recall of prospective experts and audience members (3/94).

5.0 RESEARCH, SCIENCE AND EDUCATION

5.1 Toxicology Projects

5.1.1 Immunological Mechanisms Associated with Beryllium	
Project Director:	Jean-Michel Goust, M.D.
Co-Investigator:	Philippe Arnaud, M.D., Ph.D.
Research Technician:	Clay C. Dannenhower

The aim of this project is to determine the immunological mechanisms responsible for the environmental hazard created by beryllium.

Objectives and Strategies

Objective I To determine in mice the structure of MHC class II-associated peptide(s) which would bind beryllium .

Strategy 1 This strategy is based on the following steps:

1. Purification of class II MHC molecules from susceptible (I-Ak, I-Ek) and resistant (I-Ad, I-Ed) cell lines by immunoaffinity. This requires to culture 15 to 20 liters of the cell line possessing the relevant haplotype and to purify both class II molecules using specific monoclonal antibodies immobilized on Fast Protein Liquid Chromatography (FPLC) columns.

2. Elution and characterization of the Class-II bound peptides. Steps 1 and 2 are monitored by immunofluorescence and immunochemical techniques.

3 Isolation of beryllium-binding peptide(s) by metal-ion adsorption chromatography (MIAC) on beryllium columns using FPLC.

4 Be7 the radioactive isotope of beryllium can be made available to us from the Idaho National Laboratory and should provide definitive answers regarding the identity of the beryllium-binding peptides.

5 Sequence of the dominant peptide(s) will done by tandem mass spectroscopy in the laboratory of Dr D.Knapp.

Objective II To determine the structure of MHC class II-associated peptide(s) which bind beryllium in humans.

Strategy 2 In humans suffering from Chronic Beryllium Disease (CBD) the immune response to beryllium is HLA class II-restricted and allele-specific. We will perform studies based on the results obtained with the mouse model, using a similar strategy.

1. Dr L. Newman at the National Jewish Hospital in Denver has sent us 29 coded samples which have been given to Dr Pandey. More samples will come before the end of April. By that time Dr Newman will also send Dr Goust several B cell lines from CBD patients with which we will study TNF expression in response to beryllium and its relation to the TNF alleles of these lines.

2 Human Homozygous B cell lines used as Typing Cells(HTCs) expressing the HLA-DP associated with susceptibility or resistance to CBD will be obtained from Dr Carpenter, Tissue Typing Laboratory, Harvard Medical School. Their HLA-DP will be isolated by immunoaffinity chromatography and the class II-bound peptides isolated and studied.

Milestones and Deliverables for the Third Quarter, Year 2

All column work has been delayed until the delivery of the FPLC system which occurred on March 28. It is the most significant milestone of this quarter. It will be operational starting April 4 and will enable us to complete the purification of the already produced monoclonals anti-I-Ak and I-Ad and I-Ed within a month. We should therefore be able to prepare the immunoaffinity columns for these class-II molecules in May and start their purification at that time.

Mouse model

We have produced 1.6x1010 cells from the cell line CH1 expressing the class-II molecules associated with beryllium susceptibility. Membranes bearing these molecules have been extracted and frozen at-700C. Monoclonals identifying the I-Ek molecules have been purified from 25 liters of culture. Purification of the I-Ad monoclonal is reaching completion. Eighteen liters are ready to go on the FPLC system and an additional seven liters will be produced by mid April. A monoclonal anti I-Ed is currently growing, and large sale production has started. We have received a new magnetic stirrer which enables us to grow the cell line TA27 (expressing the class-II IAd and I-Ed) at high density in spinner bottles. Large scale production will be possible, enabling us to reach 1.6x1010 in May. It will therefore be possible to start immuno-affinity purification of the mice class-II molecules in June. We are also in the process of ascertaining the amount of non-specific binding and exploring additional techniques to prevent it.

Metal ion adsorption chromatography

Normal human serum was passed on beryllium or Zinc column. We observed one protein which binds to the beryllium column but not to the zinc column. Identification of that protein will be done by 2D electrophoresis.

Human CBD

Homozygous B cell lines expressing the DP molecules associated with susceptibility or resistance to CBD are available from the 10th Histocompatibility cell lines through Dr Carpenter. These cell lines should arrive soon in our laboratory . Dr Arnaud visited Dr Ferrara in January. He will provide us with part of the human monoclonal anti-DP antibodies, but we will have to produce the bulk of what we need for immuno-affinity purification. We will use these B cell lines for three goals:

- To purify the relevant DP and extract their peptides. Recently published work shows that the concentration of Class-II bound peptides obtained from 1011 cells is from40 to 100 picomoles. It falls within the sensitivity range of the MS facility of Dr Knapp and it will be possible to analyze the peptides and to sequence the dominant ones.

- To clone the relevant DP molecules, express them in insect cells using a baculovirus system and produce recombinant DP molecules to perform binding and affinity studies.

- To determine the TNF-a allele of the B cell lines expressing CBD-associated alleles and study their TNF-a expression in response to beryllium.

Deliverables

Dr . Goust has been invited to an international meeting on Chronic Beryllium disease scheduled for November 19, 1994, in the Research Triangle Park. We have been asked to submit a manuscript of some of our findings at that time. It will be published with the proceedings of that conference in Environmental Health Perspectives, the journal of the National Institute for Occupational Safety and Health. Other deliverables are:

1. Define the binding parameters of a beryllium-affinity column for normal human serum and individualize the differences with those of other metal-affinity columns, such as Zinc and Nickel (6-94).

2. Isolate the I-Ak and I-Ek MHC molecules and elute the class-II bound peptides (6-94).

3. Use the beryllium-affinity column for separation of beryllium binding peptide(s) from other I-Ak, I-Ek-bound peptides (6-94).

4. Isolate I-Ad, I-Ed , elute the bound peptides and use MIAC to separate the beryllium-binding peptides from the other I-Ad, I-Ed bound peptides and analyze their structure by tandem mass spectrometry (7-94).

5. Produce monoclonal antibodies against CBD-associated class II HLA-DP from the human clones given us by Dr Ferrara (8-94).

6. Remove HLA-DR from the mixture of Class- II molecules before passing them over the DP column. To that effect we have started growing the hybridoma L243 which produces a monoclonal against DR molecules (6-94.)

7. Expand the relevant human HTCs , purify their class-II HLA-DP, elute the bound peptide(s) and isolate the class II-associated human peptide(s) which bind(s) beryllium (7-94/11-94). In addition we plan to use radioactive beryllium as a tracer to determine the beryllium-binding capacity of the DP-bound peptides.

8. Perform all structural studies by tandem mass spectrometry in the laboratory of Dr. D. Knapp. Although the sensitivity of the existing mass spec may not permit

sequencing of peptides present at femtomolar concentrations, we expect that the peptides responsible for an autoimmune response should be dominant and present at concentration between 40 and 100 pmoles which is detectable and at concentration high enough for sequencing.

9. Begin the production of CBD-associated the DP allelic variants associated with resistance and susceptibility. They will be used to study the possibility of direct binding of beryllium to DP and its interference with the binding of endogenous peptides, and to determine changes in their binding affinity subsequent to beryllium binding (7-94 through 10-94).

5.1.2 Assessment of Genetic Risks to Environmental Diseases

Project Director:	Janardan P. Pandey, Ph.D.
Co-Investigators:	Gillian M.P. Galbraith, M.D.
	E. Carwile LeRoy, M.D.
	Richard M. Silver, M.D.
	Hildegard R. Maricq, M.D.

The overall long-term goal of this investigation is to identify, map, and determine the mechanism of action of gene(s) responsible for susceptibility and/or resistance to environmental diseases.

Objectives and Strategies

Objective I To determine if the distribution of various genetic markers is significantly different in patient groups and controls.

Strategy 1 Blood samples will be obtained from various patient populations, such as chronic berylliosis (CBD), sarcoidosis (a disease of unknown etiology that strongly mimics CBD both in pathological and clinical presentation), and silicosis. For sarcoidosis, the controls will consist of ethnically matched healthy people. For CBD and silicosis, the control populations will be composed of ethnically matched subjects who were exposed to the environmental trigger for the same length of time as the patients but did not develop disease. Studies in mice and very recently in humans (*Science* 262:242, 1993) have clearly shown that susceptibility to CBD is MHC restricted. For this reason, candidate genes for our initial association studies will be immunologically relevant genes including HLA-DR and tumor necrosis factor a and b (chromosome 6), T cell receptor a and Gm (chromosome 14), and Km and interleukin-1a and b (chromosome 2). Both serological and molecular methodologies will be employed to study the distribution of these genetic markers.

Objective II To examine TNFa and IL-1b gene expression in monocyte/macrophage cells.

Strategy 2 Cells under study will include those obtained from the subject groups delineated in (1) and the monocytic cell line THP-1. Cells will be exposed in culture to activation with well-characterized stimuli such as lipopolysaccharide and phorbol ester, as well as beryllium. Gene expression will be monitored using molecular biological assays. In addition, the effect of extended MHC haplotypes (including the restriction fragment length polymorphisms—RFLPs—associated with the TNF locus), on gene expression will be investigated. Similarly, the possible effect of Km alleles on IL-1a and b gene expression will be studied.

Expected Dates of Major Results

1. Km typing by PCR: (12/93)
2. Determination of Gm markers by nested PCR: (3/94)
3. Determination of TNF and IL-1 alleles by PCR: (6/94)
4. Ig allotyping of serum samples from sarcoidosis patients (and other patient groups available): (3/94)
5. Isolation of DNA from serum samples: (3/94)
6. Characterization of TNF and IL-1 markers in serum DNA: (6/94)
7. Characterization of TNF and IL-1 probes: (12/93)
8. Examination of the regulation of gene expression of TNFa and IL-1b, by Northern and slot blot hybridization studies in activated monocytic cells: (6/94)

Milestones and Deliverables from Third Quarter, Year 2

1. A polymerase chain reaction (PCR) technique is being established to identify Km alleles. Km allotypes are inherited through three alleles—Km^1, $Km^{1,2}$ and Km^3 on chromosome 2. Antisera for Km 2 are extremely difficult to obtain and therefore have not been employed in most genetic studies. As a result, positivity for Km 1 in these studies includes both Km^1 and $Km^{1,2}$ alleles. Because of a strict correlation between sites for certain restriction enzymes and those responsible for the Km polymorphism, all three Km alleles can be identified unambiguously by the PCR-based methods.

    - Km Typing by PCR. We can now determine all known alleles of the Km locus by the PCR methods. This will add to our repertoire of genetic markers for studies of patients with CBD. (9/93)

    - We have Km typed a few subjects within our regional control population using the PCR technique (above). The results are in accord with those obtained by the serological method. (12/93)

2. The plasmid pcDV1 containing cDNA for human TNFa is being expanded, purified, and labeled with biotin. Similarly, biotin labeled probes for human IL-1b are being prepared from pBluescript plasmid containing a cDNA for IL-1b.

- Large scale plasmid preparations have been obtained and purified. Restriction enzyme digests of the plasmid DNAs (Pst 1 and EcoR1 digestion of pcDV1 and pBluescript, respectively) and subsequent Southern gel eletrophoresis revealed cDNA inserts of expected size. Plasmid DNA was labeled with biotin by nick translation; Southern hybridization studies with these labeled DNAs confirmed the specificity of the probes.

- Examination of the regulation of gene expression of TNFa and IL-1b, by Northern and slot blot hybridization studies in activated monocytic cells: Initial hybridization experiments have shown that the human monocytic cell line, THP-1, responds to exposure to lipopolysaccharide (LPS) by accumulation of TNFa mRNA in a dose-dependent manner, and that this is accompanied by the secretion of large amounts of the cytokine, detected by ELISA. Similar experiments using another cell line, U937, gave negative results.

  Preliminary studies of the direct effect of beryllium ions on gene expression have also been performed using THP-1 cells. Data obtained from two experiments indicate that exposure to beryllium can induce the accumulation of TNFa mRNA, and that this effect is enhanced by the presence of fluoride ions. ELISAs for quantitation of TNFa and IL-1b in the culture media of these experiments showed release of both cytokines. (9/93)

- Characterization of the TNF-a gene expression in human monocytic cell lines has included time course and dose response studies. Initial experiments using alveolar macrophages obtained from a patient with sarcoidosis showed high levels of TNF-a mRNA expression and cytokine release, which suggests that these cells are activated *in situ*. However, exposure of the cells to lipopolysaccharide resulted in further production of the cytokine. (12/93)

3. The genes for tumor necrosis factor (TNF) have been localized within a 7-kb repertoire of genetic markers for studies of patients with CBD. So far we have studied 11 controls, and the distribution of the three genotypes in these subjects is in accord with that predicted by the Hardy-Weinberg law. (9/93)

   - We have characterized over 61 patients with IgA nephropathy and 62 ethnically matched controls for the two TNF-a alleles. The results showed that the distribution of the three genotypes was similar in bothgroups. (12/93)

4. Silicosis, a chronic respiratory disease, is caused by prolonged inhalation of silica particles. However, not all individuals exposed to silica dust develop severe lung fibrosis, suggesting the involvement of genetic factors in susceptibility to this disease. A recent study (*Am. J. Resp. Cell Biol.* 8:106-111, 1993) has shown that one of the genes responsible for the disease may be closely linked to the HLA-B locus. We plan to study whether Gm, Km, and TNF-a genes also influence susceptibility to silicosis. We will also determine possible interactive effects of these genetic markers.

- Gm and Km allotyping has been performed in 66 silicosis patients and 97 ethnically matched controls from Japan. Preliminary analysis shows an increased frequency of certain phenotypes in patients as compared to the controls.

5. The newly described biallelic polymorphism of the TNF-a gene is in the promotor region of this locus. For this reason, we hypothesize that the two alleles may play a regulatory role in the expression of TNF-a.

   - Expanded studies of TNF-a alleles and cytokine production in our control population have been performed.

6. Blood samples received from our collaborators are usually in the form of serum. It is necessary to develop techniques to isolate DNA from sera for molecular genetic characterization.

   - The isolation of DNA from serum samples has been achieved.

7. Serological determination of Gm allotypes is fraught with problems such as the limited availability of monospecific antisera and the presence of interfering antibodies which can cause false negative results. PCR based molecular methods of Gm allotyping circumvent these problems.

   - We have established the methodology to determine Gm 3 and 17 by nested PCR.

Milestones and Deliverables Planned for the Fourth Quarter

8. We have received coded CBD and control cell samples from Dr. Newman of Denver, and serum samples from Dr. Saltini of Italy. Genomic DNA samples from CBD patients and controls will be sent by Dr. Saltini in the near future.We intend to characterize these samples with respect to Gm, Km and TNF loci.

   - Isolation of genomic DNA from cell samples and determination of TNF alleles will be performed.
   - Serologic determination of Gm and Km allotypes will be performed on serum samples.

9. Genotyping by PCR using serum

   - A large, previously HLA typed control population will be characterized with respect to the TNF-a alleles by PCR.

5.1.3	Identification of Trichloroethylene-Hemoglobin Adducts for Use in the Development of an Immunological Assay to Assess Trichloroethylene Exposure in Humans
Project Director:	David C. McMillan, Ph.D.

Description

1,1,2-Trichloroethylene (TCE) is a commonly used industrial solvent and has become a common environmental contaminant. At DOE sites it is the most abundant chlorinated hydrocarbon contaminant, being present in ground water and soils and sediment in some areas at levels thousands of times to millions of times higher, respectively, than EPA's regulatory maximum level for drinking water.

The main target organ for TCE toxicity is the liver. Chronic exposure to TCE has been shown to cause hepatic carcinomas in $B6C3F_1$ mice, but not in Osborne-Mendel rats. In addition TCE exposure has produced lymphomas in hamsters, lung tumors in ICR rats and renal tumors in Fischer 344 rats. These tumors, however have not been consistently observed in other rodent species and strains.

Macromolecular adducts have received considerable attention as possible internal dosimeters (i.e., biomarkers of exposure) for carcinogens requiring metabolic activation. This method is thought to be superior to other indices of exposure (e.g., measurement of urinary metabolites) since it has the potential for assessing the "biologically effective dose", and because exposure can be detected for relatively long periods of time after subjects have been removed from the source of exposure.

Several investigators have reported the association of radiolabeled TCE metabolites to cellular macromolecules (both DNA and protein) in rats and mice. Recently, TCE metabolites were shown to bind covalently to both hemoglobin and serum albumin, proteins that have been used as dosimeters for a variety of chemical carcinogens. However, the specific adducts have not been identified, and there is as yet no convenient method for assessing human exposure to TCE. We propose to identify TCE-hemoglobin adducts using tandem mass spectrometry. When the specific protein adducts are identified, they will be prepared in vitro and used as immunogens to raise antibodies in rabbits to TCE-protein adducts. Once this is accomplished, a rapid and sensitive immunoassay will be developed to detect TCE adducts in human blood samples.

Significance:

This project should provide useful information in assessing the risk TCE poses as a human health hazard. Furthermore, this project will allow us to optimize the methodology necessary to develop biomarkers for additional chemicals of interest at many hazardous waste sites.

Objectives:

1. To identify and structurally characterize human hemoglobin adducts derived from exposure to TCE.

2. To prepare immunogens and generate antisera to these biomarkers for development and application of immunoassays for the biomarkers.

3. To characterize protein adduct biomarkers of exposure to additional chemicals of relevance to DOE sites and develop antisera to these biomarkers.

Milestones from Third Quarter, Year 2:

1. Obtained human hemoglobin from new source (whole blood from volunteer). This preparation was purified by ammonium sulfate precipitation and pressure dialysis.

2. Mass spectral analysis of unmodified hemoglobin from new source completed (peptide map completed).

3. Reaction of TCE metabolite derivative (dichloroacetic anhydride) with hemolysate and mass spectral analysis completed. No adducts were detected under these experimental conditions.

4. Synthesis of dichloroacetyl lysine begun (used as an inhibitor for characterization of antibody to TCE raised by Dr. Neil Pumford).

Milestones Planned for Fourth Quarter:

The above milestones will be continued during the next quarter. Preparation of manuscript (deliverable) for annual report will be initiated.

5.1.4 Species Comparison of Trichloroethylene-Induced Peroxisome Proliferation and Induction of DNA Syntheses

Project Director: JoEllyn M. McMillan, Ph.D.

Description

1,1,2-Trichloroethylene (TCE) is a commonly used industrial solvent and has become a common environmental contaminant. At DOE sites it is the most abundant chlorinated hydrocarbon contaminant, being present in ground water and soils and sediment in some areas at levels thousands of times to millions of times higher, respectively, than EPA's regulatory maximum level for drinking water.

The main target organ for TCE toxicity is the liver. Chronic exposure to TCE has been shown to cause hepatic carcinomas in $B6C3F_1$ mice, but not in Osborne-Mendel rats. In addition TCE exposure has produced lymphomas in hamsters, lung tumors in ICR rats and renal tumors in Fischer 344 rats. These tumors, however have not been consistently observed in other rodent species and strains.

TCE falls into a category of compounds known as peroxisome proliferators. Peroxisome proliferators induce a characteristic pattern of primarily hepatocellular responses. Hepatocarcinogenesis is a common property of all peroxisome proliferators tested thus far; however, this response is not usually associated with direct genotoxic activity of the compound. Increased production of hydrogen peroxide, which may cause indirect gentoxicity, and the propensity of these compounds to induce hepatocyte replication have been argued to contribute to their carcinogenic activity.

TCE-induced peroxisome proliferation has been demonstrated in rats and mice and in mouse hepatocyte cultures. We propose to examine the peroxisome proliferative and mitogenic activity of TCE and its proposed hepatotoxic metabolites, trichloroacetic acid (TCA) and dichloroacetic acid (DCA), by utilizing hepatocyte cultures from $B6C3F_1$ mice and Osborne Mendel rats and to compare the response in these cultured cells to that in a human liver cell line and/or human hepatocytes. The results from these studies would provide information on the relative susceptibility of human, rat and mouse liver to the potential hepatocarcinogenic activity of TCE.

Significance:

This project should provide useful information in assessing the risk TCE poses as a human health hazard, both at DOE sites and in surrounding areas where there is ground water contamination.

Objectives

1. To determine the dose/response relationship of TCE and its toxic metabolites to induce peroxisome proliferation and DNA synthesis in rat and mouse hepatocyte cultures.

2. To determine the ability of TCE and its toxic metabolites to induce peroxisome proliferation and DNA synthesis in human liver cell lines and/or human hepatocyte cultures.

Milestones and Deliverables from Third Quarter, Year 2

1. Optimize assay for determining DNA synthesis
   - Assay protocol developed for measuring DNA synthesis

2. Optimize hepatocyte culture conditions for studies on TCE-induced peroxisome proliferation

3. Optimize HepG2/Hep3B culture conditions for studies on TCE-induced peroxisome proliferation

4. Obtain information on obtaining human liver sections (for isolation of hepatocytes) from a source at MUSC.
   - Have approached Dr. Adrien Rubin, the new director of MUSC's liver transplant unit, about the possibility of obtaining human liver samples for isolation of hepatocytes.

Milestones and Deliverables Planned for the Fourth Quarter:

5. Compare induction of peroxisome proliferation by TCE with that of a known peroxisome proliferator (*e.g.*. clofibrate)
   - Data on the dose-response relationship for peroxisome proliferation in rat and mouse hepatocytes (6/94)
   - Data on the dose-response relationship for peroxisome proliferation in HepG2 cells (6/94)
   - Comparative data for clofibrate in rat and mouse hepatocytes and in HepG2 and/or Hep3B cells(6/94)

6: Compare the induction of DNA synthesis by TCE with that of a known mitogen (*e.g.*. epidermal growth factor)
   - Data on the dose-response relationship for induction of DNA synthesis in rat and mouse hepatocytes (6/94)
   - Data on the dose-response relationship for induction of DNA synthesis in HepG2 cells (6/94)
   - Comparative data for epidermal (or hepatocyte) growth factor in rat and mouse hepatocytes and in HepG2 and/or Hep3B cells (6/94)

5.1.5 Mass Spectrometric Analysis of Proteins and Peptides in Relation to: Studies of Metal Induced Autoimmune Diseases and Studies of Biomarkers of Toxic Chemical Exposure

Project Director : Daniel R. Knapp, Ph.D.
Research Associate: Mark Busman, Ph.D.

Description

This project entails development of online high performance liquid chromatography (HPLC) - electrospray ionization (ESI) - triple quadrupole tandem mass spectrometry (MS/MS) analysis of peptides in support of the two projects listed above. The major equipment being used for this project has been acquired with other than EHAP funding and none of the personnel time is supported by the EHAP grant. EHAP funding will be used to acquire the needed HPLC equipment.

Milestones and Deliverables from Third Quarter, Year 2:

1. Implementation of a new electrospray ion source on the Nermag R30-10 triple quadrupole tandem mass spectrometer to permit online HPLC-MS analysis.
   - We have determined that the newly designed and constructed ESI source on the Nermag instrument does not appear to be capable of the sensitivity required for the online HPLC-MS analysis of MHC bound antigenic peptide mixtures in the quantities originally envisioned. However, we still should be able to provide the needed analyses for samples enriched in specific peptides if sufficient sample is available.

2. Implementation of a new Macintosh based data system on the Nermag R30-10 for instrument control and data acquisition.
   - Construction is still underway on interface enhancements to enable computer control of quadrupole resolution and offset as well as optical element potentials.

3. Assembly of microbore/capillary HPLC system.
   - Authorization was obtained to proceed with the purchase of this equipment, however it was determined that the procurement would have to be done by competitive bidding. Bid specifications were developed, bids were invited and received, and a decision was made on the purchase. We are now awaiting release of the purchase order by the procurement department

4. Interfacing of microbore/capillary HPLC to the electrospray ion source on the Nermag R30-10.
   - Awaiting receipt of HPLC hardware.

5. Implementation of flow-FAB ion source on the JEOL HX110/HX110 four sector tandem mass spectrometer.
   - Flow FAB ion source has been completed and installed. Operation is limited by instability of vacuum under flow FAB conditions. This will be alleviated by installation of a liquid nitrogen cold trap. This installation is awaiting arrival of parts.

6. Interfacing of microbore/capillary HPLC to the flow FAB ion source on the JEOL HX110/HX110.
   - Awaiting receipt of HPLC hardware.

7. Synthesis of model antigenic peptides for analytical methods development.
   - No work yet initiated.

8. Implementation of online HPLC-MS and MS-MS analysis of peptide in mixtures.
   - No work yet initiated.

9. Establishment of sensitivity limits for online HPLC-MS and MS-MS analysis of peptides.
   - No work yet initiated.

10. Analysis of HLA presented antigenic peptides from Beryllium autoimmune disease studies.
    - No work yet initiated.

11. Analysis of tryptic digest peptide mixtures from hemoblobin adducted with TCE metabolites.
    - Work has been initiated on fractions collected by offline HPLC (see D. McMillan progress report).

Milestones and Deliverables planned for Fourth Quarter:

Work will be pursued on Milestones 4, 5, 6, 8, 9, and 11. Expected deliverables will include a paper on hemoglobin adducts to be submitted in collaboration with D. McMillan.

5.2 Risk Assessment Projects

5.2.1 Low Dose-Rate Radiation Health Effects

Project Director:	David G. Hoel
Research Associate:	Grace Lossman
Research Associate:	Zhen Zhang

Description

In the evaluation of external ionizing radiation exposure to man, all of the health risk assessments are based on acute exposures. It has been known from animal studies that often times for the same total dose, the toxic effects of radiation are less if the exposure is given continually at a low dose-rate. Estimates of the reduction in risks have ranged from a factor of 2 to 10. Obviously, this would greatly impact the strategies for clean-up of radioactive materials and the level of permissible exposure to workers.

Goals, Objectives and Strategies

Goals: To determine dose-rate effectiveness factors for various cancers in rodent studies after gamma or neutron exposure. To determine relative biological effectiveness of neutrons in rodent cancer studies. Relate the rodent models to human epidemiological data.

Objectives and Strategies: To study this question, it is necessary to bring together large amounts of animal studies that have been conducted through the years by DOE and compare chronic vs. acute exposures using statistical cancer models for the analysis. One would then be able to project the effects of estimated human cancer risk at low dose-rate exposures. Connected with this analysis, it is also possible to work out risk assessments for neutron exposure for which there is little or no human data. This work would again depend upon DOE experimental information. This research would be carried out collaboratively with scientists at the Argonne National Laboratory and the University of Tennessee.

Year 1: (Completed)

Objectives:

- Design and select cancer models
- Select appropriate data bases

Strategies:

- Study appropriateness of human cancer models for rodents' analysis
- Obtain and prepare Argonne rodent data bases for analysis

Year 2:

Objectives:

- Begin dose-rate modeling
- Study graphical model displays

Strategies:

- Model several gamma dose-rate experiments
- Begin graphical presentations

Milestones and Deliverables from Third Quarter, Year 2

1. Total tumors and connective tissue tumors have been fitted for both gamma and neutron exposures for several dose-rates. Step function models were employed for these fits.
2. Epithelial tumors have received a preliminary analysis using step functions.

Milestones and Deliverables planned for Fourth Quarter

1. A report of models so far completed will be produced.
2. Dose-rate models will be completed for connective tissue tumors.
3. RBE's for neutrons will be completed for connective tissue tumors.

5.2.2 Environmental Risk Perception in Defined Populations	
Project Leaders:	Daniel Lackland, Ph.D. John Dunbar, Ph.D. David Hoel, Ph.D.

Description

Risk perception is an important consideration in environmental restoration and cleanup standards, as well as being a key component of risk assessment. The quantification of perceived risks, risk awareness and knowledge of health hazards is critical to the determination of public-acceptable levels of environmental contamination. The development and implementation of methodologies are necessary preludes to any comprehensive environmental hazard and risk assessment program.

Goal, Objectives and Strategies

Goal: To develop, implement and maintain a comprehensive environmental risk perception assessment center and methodology, capable of rapid ascertainment evaluation and analyses of population data.

This program is designed to be a major resource for Department of Energy sites as well as other groups involved in the decision process for environmental remediation and restoration. Furthermore, the project will provide timely feedback of community and population-based findings to concerned parties, including the Crossroads and risk assessment programs.

Objectives

- To develop methodology for the measurement of knowledge, awareness and attitudes with regards to environmental hazards risks to human health.
- To quantify these measures and construct a perceived risk index.
- To estimate levels of acceptable risk in the population.

Strategies

- Inventory of existing perceived risk assessment programs.
- Assessment of methodologies used to incorporate risk perception in decision making.
- Comprehensive review of literature on risk perception.
- Development of population pilot project.
- Development of an advisory committee.

Milestones and Deliverables from Third Quarter, Year 2

1. Pilot population survey - The survey of 1,000 households of residents in Georgia and South Carolina regarding perceived risks was analyzed. In addition to analyzing variation in risk perceptions proximal to the Savannah River Site, an assessment of perception by race was completed. These results were presented:
   - NIH meeting on environmental justice;
   - EHAP seminar.

2. Expert advisory committee - The first meeting of the expert advisory committee was held February 24 and 25. The two-day meeting and reception was attended by 35 additional individuals. Committee members provided valuable recommendations and advice. The committee was available for numerous secondary meetings to discuss plans and activities. The Committee will meet twice a year to assess the program. Members of the committee include:
   - Dr. Jeff Lybarger, ATSDR
   - Dr. Max Lum, ATSDR
   - Dr. Larry Needham, CDC
   - Dr. Clark Heath, American Cancer Society
   - Dr. Roy Eckart, University of Cincinnati
   - Dr. Todd Stong, Coleman Research
   - Dr. David McCallum, Society for Risk Analysis
   - Dr. Pat O'Neil, MUSC
   - Dr. Bernd Grosche, German Radiation Health Institute.

3. Presentations at:
   - EHAP seminar on epidemiology
   - Stone Container (Savannah)
   - Union Camp (Savannah).

4. Meeting with Dr. Richard Selastras to discuss assessment of airline pilots and the health effects of low level (cosmic) radiation.

Milestones and Deliverables Planned for Fourth Quarter

1. Pilot Population Survey

- Manuscripts on variation proximal to SRS
- Perception variation by race.

2. Expert Advisory Committee
   - Notes and recommendations will be written in a technical report.

3. Calculation and communication of health risks associated with current and anticipated tritium releases at SRS. In the second quarter, a three person subcommittee of the Expert Advisory Committee was named to develop and oversee a project to promote public awareness about health effects associated with current and anticipated future tritium releases from the SRS enterprise. The project will be developed around three tasks:
   1. Define the problem and the scope, determine tritium sources and collect data on current releases and future estimates.
   2. Calculate dose and health risk.
   3. Communicate the findings to the public.

   By the end of the fourth quarter, a substantive draft will be submitted.

5.3 Information Support and Access Systems	
Director:	Tom Basler, Ph.D.
Systems Analysis:	Richard Gadsden, CCIT
Manager/Coordinator:	Jack Davis
Biomolecular Computing:	Starr Hazard
Word Processing Specialist:	Carol Savage

There are three main thrusts of the Information Support Project and one operational responsibility:

- build and maintain the basic computer and network structure for information handling,
- support of the Education Initiative,
- support of the Seminars, Science, & Risk Assessment, and
- operational support of EHAP overall internal computing and communications.

The following project description addresses project execution through its support of the other education, science, and Crossroads projects.

Project Goals, Objectives and Strategies

The objective of this project is to support the information, communication, and computational needs of the outreach, education, and research tasks encompassed by EHAP. The basic strategy involves two primary components. First, the Information Systems Design Group built the specifications and architecture for computer systems that are capable, generally, of the computation and communication necessary to achieve EHAP goals. During Year 1 of the program, core equipment, based on the design architecture,

was purchased. Installation of this equipment continues in Year 2. The major focus during the second year of the grant is to generate preliminary designs of an information access system which will serve researchers, health practitioners, and other environmental professionals. Two basic tenets provide focus for the information access system design. First, no new databases or other information systems are being created -- the system's function is to provide easy, user-friendly access to a broad range of data sources that already exist. Second, we'll be using data fusion techniques to assist the user in identifying and retrieving as much relevant data as is possible from a wide range of sources. By the end of the second year of the grant, we'll have completed extensive surveys of users to establish needs, surveys of information sources, and a first-cut prototype to prove the design concepts.

Milestones Achieved

1. The MUSC Gopher was "registered" February 1, 1994 and announced for us by all local and national users April 1, 1994. The first major day-long training day is scheduled for April 7, 1994 in the Library microcomputer teaching facilities. These formal sessions included on-campus interactive television broadcasts to other parts of the State of South Carolina. The MUSC Gopher is particularly robust in the folders marked EHAP and LIBRARY and is expected to see further development throughout Spring and Summer of 1994.
2. Choice and discovery work has been made in the area of databases to be provided for both MUSC and EHAP rather than as one program not in phase with the other. A navigator/front end has been chosen and tested. Networking capabilities are now fully operational and tested. Interface with local colleges, state-wide networks, the Internet and various other typical navigators (i.e., Gopher) is complete. Although additional databases will be chosen and mounted or accessed due to the findings of the "One-door-access" system being developed by Coleman Research Corp., the following list of databases were being implemented during January 1994 to be fully available by June, 1994.

Mounted locally (MUSC in Charleston) within the Information System

MEDLINE
miniMEDLINE
Current Contents
- Life Sciences
- Clinical Medicine
- Agriculture, Biology
- Environmental Sciences
- Physical/Chemical Sciences

CancerLIT
CINAHL
Health Administration
PsycInfo

Accessed remotely through the Information System, Federal Register

CoastNet
- Library catalogs of local colleges (Charleston, Charleston Southern, Citadel)
- Applied Science &^ Technology Index

Art Index
Business Periodicals Index
Humanities Index
General Science Index
Readers Guide to Periodical Literature

Accessed remotely through the Information System & Agreements with Georgetown University Medical Center

CINAHL
MicroMedex

Accessed through other methods.

TOXNET
TOXLINE, etc.

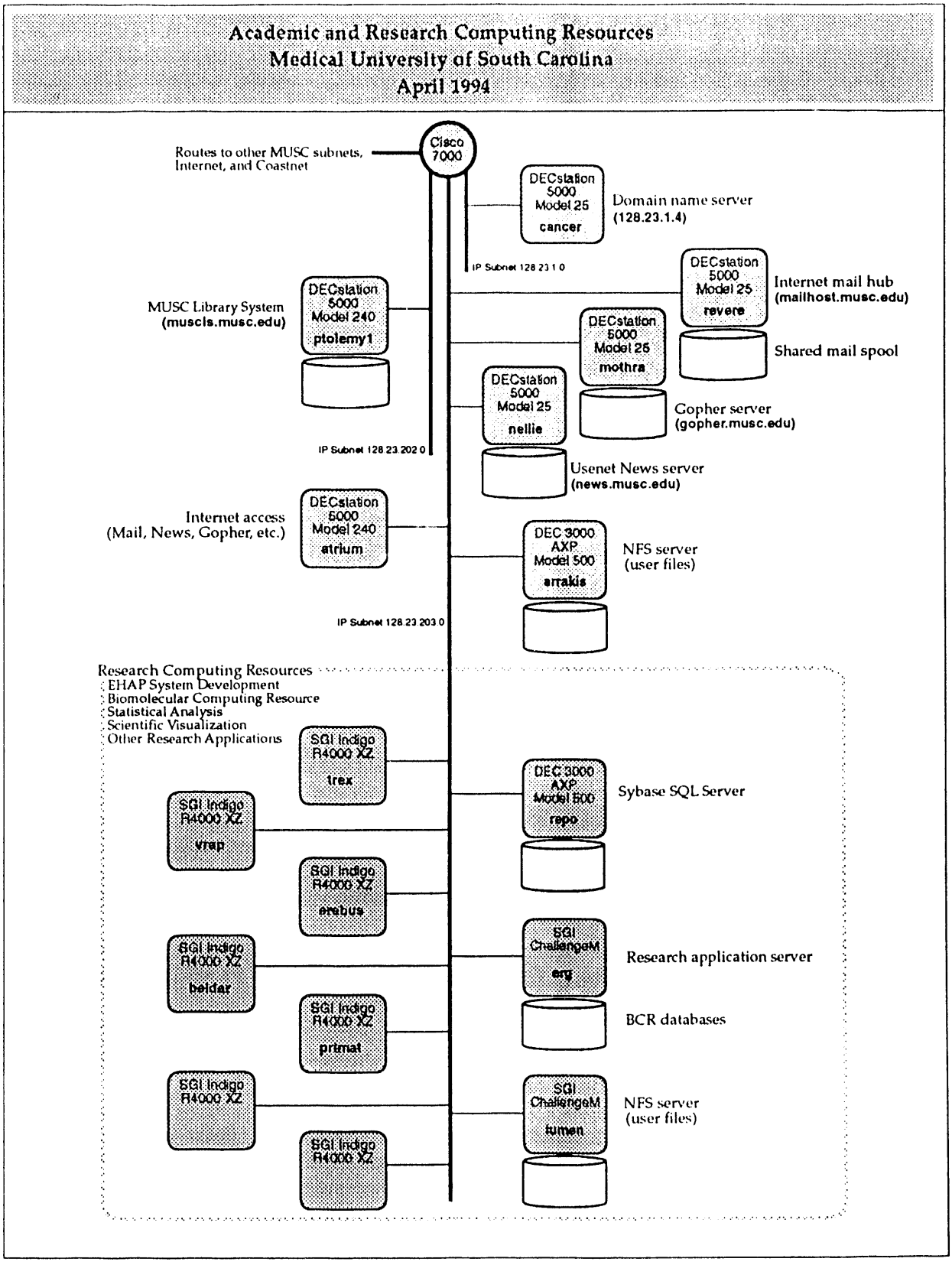
3. A major focus of Year 1 and Year 2 activities has been the design and installation of new hardware computing resources. This activity has been closely coordinated with grant efforts to improve the research computing resources and to develop the "one-door" access system. A diagram of the new academic and research computing resources at the university follows. During the quarter:
   - completed installation and setup of master (lumen) and slave (erg,arrakis) servers to provide NIS services network-wide,
   - completed installation and setup of NFS servers (lumen, arrakis) to provide "home directory" and software repository services to all workstations on the network (2),
   - implemented new Internet services such as Gopher, electronic mail, and Usenet News, and installed and set up client software on SGI workstations to access these services, and
   - finalized plans for deployment of SGI workstations to University departments.

4. A preliminary needs assessment survey first draft report has been completed. The final report is planned for completion by the end of next quarter as well as the information system survey results.

Milestones and Deliverables Planned

Milestones planned for next quarter deal primarily with the continued work on the needs assessment surveys and the information access system prototype development. In specific:

- deployment of SGI workstations in University departments and initiation of training and support of EHAP researchers,
- completion and final report of the needs assessment survey,
- completion and final report of the information system survey, and
- completion and demonstration of the first "one-door" access system prototype.


Academic and Research Computing Resources
Medical University of South Carolina
April 1994
Routes to other MUSC subnets, Internet, and Coastnet
Cisco 7000
DECstation 5000 Model 25 cancer
Domain name server (128.23.1.4)
IP Subnet 128.23.1.0
DECstation 5000 Model 25 revere
Internet mail hub (mailhost.musc.edu)
Shared mail spool
MUSC Library System (muscls.musc.edu)
DECstation 5000 Model 240 ptolemy1
DECstation 5000 Model 25 mothra
Gopher server (gopher.musc.edu)
DECstation 5000 Model 25 nellie
Usenet News server (news.musc.edu)
IP Subnet 128.23.202.0
Internet access (Mail, News, Gopher, etc.)
DECstation 5000 Model 240 atrium
DEC 3000 AXP Model 500 arrakis
NFS server (user files)
IP Subnet 128.23.203.0
Research Computing Resources
EHAP System Development
Biomolecular Computing Resource
Statistical Analysis
Scientific Visualization
Other Research Applications
SGI Indigo R4000 XZ trex
DEC 3000 AXP Model 800 repo
Sybase SQL Server
SGI Indigo R4000 XZ vrap
SGI Indigo R4000 XZ erebus
SGI Indigo R4000 XZ beldar
SGI ChallengeM erg
Research application server
BCR databases
SGI Indigo R4000 XZ primat
SGI Indigo R4000 XZ
SGI ChallengeM lumen
NFS server (user files)
SGI Indigo R4000 XZ

5.4 Education

5.4.1 Environmental Medicine & Risk Communication: Curriculum and a Professional Support Network - Department of Family Medicine	
Director:	Stanley H. Schuman, M.D., Dr. P.H.
Project Administrator:	Samuel T. Caldwell, M.A.
Staff Dev.& Training Coordinator:	Larry H. Spell, M.S.
Staff Dev.& Training Specialist:	Jan A. Lay, M.S.
Administrative Assistant:	JoAnn Retter

The objectives of this project are to: 1) develop environmental medicine curriculum for the SC Statewide Family Practice Residency System (SCSFPRS), and 2) develop a consultative/support network in environmental medicine for the faculty and residents of the SCSFPRS.

Milestones and Deliverables from Third Quarter, Year 2

Curriculum

1. The EMCC held its third workshop March 15-16, 1994 in North Myrtle Beach, SC. The meeting agenda included review and comment on the following five environmental and occupational medicine (EOM) longitudinal curriculum modules. Module 6, EOM Site Visit, was not ready for review. Each module consists of a slide lecture with script and an interactive computer program.
   1) EOM History for Family Physicians,
   2) Communicating Environmental & Occupational Risks to Patients: A Guide for the Family Physician,
   3) Family Physician's Response to the EOM Patient: Seven Steps to a Successful Encounter,
   4) EOM Resources for the Family Physicians, and
   5) EOM in Private Practice: Choices for the Family Physician.

   The committee voted to merge two of the modules (modules 2 and 3 above), thus revising the curriculum matrix:
   - Environmental & Occupational Medicine Curriculum, Environmental Medicine Curriculum Committee / Statewide Family Practice Residency System (Revised 3/11/94).

   Following the meeting the project staff began to incorporate the committee's comments and suggestions into the curriculum modules.

2. The monthly EMCC newsletter, *Environmental Medicine Update*, was published January through March 1994. The objectives of the newsletter are to report on committee activities and to stimulate committee members concerning recent developments in environmental medicine.

3. Project staff continued the EOM literature retrieval service for the EMCC. Relevant data bases are searched monthly for topics of interest to the committee

members. A listing of articles is compiled and forwarded to each member to select those articles he would like to have copies. The listings are returned to the staff and a package of the selected articles are then forwarded to the member (ongoing).

4. Seventeen EOM lectures were presented during the period.
   - Lectures described in the January - March 1994 Summary Reports.

Consultative and Support Network

1. Monthly environmental/occupational medicine literature review for pertinent articles to be added to the project's computerized data base continued (ongoing).

2. Staff members consulted on 40 environmental/occupational cases during the period.
   - Cases described in the January - March 1994 Summary Reports.

3. At the March 11 meeting, the EMCC accepted Dr. Schuman's proposal to use the resources of the Occupational and Environmental Medicine Office (OEMO) for consultation and clinical case research on EOM. These services will be provided at no charge to the residents, faculty and staff of the Statewide Family Practice Residency System. Rotary file and business cards describing the service are being developed.

Milestone and Deliverables Planned for Fourth Quarter

1. Finalize, produce, and distribute to the EMCC Version 1.0 of the five longitudinal core curriculum modules.

2. Produce and distribute business and rotary file cards to the Statewide Family Practice Residency System which describe the consultative and case research services of the OEMO.

3. Outlines for the EOM elective curriculum.

5.4.2 Environmental Hazards Assessment and Education Program in Pharmacy Graduate Education in Risk Assessment

Director:	Rosalie Crouch, Ph. D.
Research Director:	G. Patrick Meier, Ph. D.
Research Associate:	Catherine Musham, Ph. D.
Research Associate:	Debrah Carson, Pharm. D., BCPS
Research Associate:	Terry Ocheltree, B. S. Pharmacy.
Research Associate:	Dylan Holmes, B. S.

Description

There are two components to this project.

A) We are developing an instrument for assessing the current and future environmental health activities and needs of both practicing pharmacists and

pharmacy educational programs within South Carolina. The specific objectives are to develop an assessment tool, implement the tool, analyze the results, and report the conclusions both as a report to EHAP and as a paper.

B) I am developing an existing undergraduate course to include mechanistic bio-organic chemistry as it is applied to toxicology, discuss the concept of risk assessment, and introduce information about available on-line environmental health related databases. The course is currently focused on the nomenclature and functional group chemistry of organic chemistry. The specific objectives are to expand on the current course material, test on the presented material, and assess the students' opinions concerning the inclusion of environmental health materials in the course curriculum.

The rational for these programs is that pharmacists are considered by the general population to be one of the most trustworthy professional groups and they are one of the first groups of health car providers that the common population comes to for minor health problems. Thus they are an important health care and information providing group for the public and as such should have a good background in the chemistry, toxicology, and risk assessment of environmental hazards.

Milestones and Deliverables Achieved in Third Quarter, Year 2

1) Environmental Hazards Assessment Program
   - The information from the final survey has been cataloged and the return rate is better than 42 %.
   - The survey data was entered into a data base.
   - The data base has been analyzed mathematically (the results are included with this report).
   - The results have been partially conceptually analyzed.
   - The data has been delivered to Glenn Fleming (EHAP), and he and his group are involved in the conceptual analysis.

2) BS Level Medicinal Chemistry/ Environmental Health Course Development. This project has been completed.

Milestones and Deliverables to be Completed in the Fourth Quarter:

- The data from the survey will be conceptually and statistically analyzed.
- The results of the data analysis will be written up and delivered to the EHAP.
- The data and analysis will be presented at a meeting (tentatively the AACP meeting in July 1994).
- The data and analysis will be submitted for publication.
- The completed compiled data and analysis will be sent to the pharmacists who requested this information (389 of 410).

5.4.3 Graduate Education in Risk Assessment	
Project Director:	Dr. Rosalie Crouch, Dean College of Graduate Studies

Description

An essential part of the program in environmental risk assessment is the educational component. This task is concerned with establishing strong academic graduate programs at the masters and doctoral levels with both address the needs of governmental agencies and private industry and respond to public concerns. These programs will address the void of graduates who have the combination of some understanding of science, risk analysis and the policy process. Graduates at the doctoral level will have, in addition, considerable expertise in a defined area which they have selected for their dissertation. Attention will be given in future years of the project to undergraduate environmental studies and introduction of these topics at the primary and secondary school levels.

Goal: To develop outstanding academic programs at the masters and doctoral levels which educate the student in the fundamentals of environmental risk, policy and science with a specialization in one of these areas.

Milestones and Deliverables Achieved

1. Brochure designed for the Master in Environmental Studies Program.
   - 5,000 brochures mailed to various departments in institutions throughout the United States for the purpose of recruitment.

2. Recruitment of environmental microbiologist and risk analyst faculty
   - Advertisement for position placed in SCIENCE
   - Three candidates interviewed for the position
   - Dr. Pamela Morris selected

3. Formation of an external advisory council to provide annual guidance on the environmental graduate programs.
   - In progress

4. Recruitment for Summer Undergraduate Research Program
   - Received 280 applications and 10 positions awarded.

Milestones and Deliverables Planned for the Fourth Quarter

1. Continue to develop course curriculum for courses to be offered by the College of Charleston for the Masters in Environmental Studies Program.

2. Development of an environmental (occupational) health nurse practitioner track in the Master's degree Primary Care Nurse Practitioner Program. Also continuing

educational (CE) workshops targeted to nurses and undergraduate and graduate faculty.

3. Poster for the Master of Science in Environmental Studies Program designed and mass mailout planned for recruitment for the Spring 1995 Semester.

4. Admissions Committee appointed for the Master of Science in Environmental Studies Program.

5. Initiate Summer Undergraduate Research Program beginning June 1 through August 5.

5.4.4 Department of Environmental Health Sciences (DEHS) - Education and Training Initiative	
Project Director:	Janet Z. Temple, Ph.D.
Assistant Director	Mike Reed
Faculty	Robert Kennedy, Ph.D.
Faculty	William Hotle
Faculty	Nancy Kierstead
Administrative Specialist	Gerri Hollis
Accounting Tech	Paula Butler

Description

The primary objective of this task is to address worker and management training needs in a rapidly changing environment. One of the environmental industry's missions is to ensure that resources are available to assure the current and future workforce has the skills, knowledge and abilities to carry out its mission today and in the future; and to ensure that all groups within our society participate in the successful cleanup activities of environmentally hazardous sites. Adequate training to address the risks to the public, the workers, and the environment is essential for those workers and managers who will be involved with environmental cleanup and restoration issues within government, business, and industry.

The Department of Environmental Health Sciences is involved in the Education and Training Initiative. An Advisory Committee has been established to render guidance to this task. It includes representatives from EPA, OSHA, DOE, DOD, unions, educators, public interest groups and the healthcare community. The third meeting of the Advisory Committee is scheduled for May 17, 1994 in Charleston, South Carolina.

A needs assessment instrument has been developed to secure profiles of mid and upper level managers and their training needs relating to risk.

Two to three Professional Development seminars will be designed and developed during year two. The programs will be two to three days in length, and will include 1) Concepts in Risk Analysis - an introduction to risk assessment methods for mid and upper level

managers, 2) Environmental Risk Management - focusing on the use of risk assessment in the decision making process, and 3) Risk communication/public participation.

The Concepts of Risk Assessment seminar has been finalized and was presented to EHAP and MUSC employees on February 1 and 2 in Charleston, South Carolina. The course was well received and beneficial comments were provided by those who attended.

Milestones and Deliverables Achieved in Third Quarter, Year 2

Planning/Administration

1) Networking to examine training needs of government facilities as well as industry. (Attendees)
   - January 20-22, 1994 Hanford Summit II, Seattle, Washington. Dr Jan Temple is a member of the Training and Education Committee.
   - February 13-16, 1994. American hospital Association Meeting, Lake Buena Vista, Florida. Dr. Jan Temple presented two programs 1) "The Risk Analysis Process in Environmental Decision Making," and 2) "EPA Regulatory Update."
   - American Hospital Association 4th National Symposium and Trade Exhibition on Healthcare Safety and the Environment February 13-16, 1994 in Lake Buena Vista, FL.
   - March 12-16, 1994. National Environmental Information Association annual meeting, Mission Valley, California. "EM 94". Presentation by Dr. Jan Temple, Michael Reed and Jim Graves concerning Environmental Health and Risk Communication.

2) Maintain an off site library to house environmental risk assessment, management, and communication information.
   - The off-site library has been established and is currently housed in Harborview Office Towers , 601, Conference Room.

3) Submitted Second Quarter Report for EHAP Task 5, January 12, 1994.
   - Deliverables include report previously submitted.

4) Joined in the development of Integrated Course Development for Environmental Engineering Courses for the Charleston Naval Shipyard.
   - Closure Engineering Division of the Charleston Naval Shipyard has arranged with the Medical University of South Carolina to provide a series of courses on topics of interest to the Shipyard. The Department of Environmental Health will be providing courses on Risk Analysis, Toxicology, and Health Concerns of PCBs.

Needs Assessment Instrument

1) A revised needs assessment instrument has been developed to better ascertain the level of risk awareness of the subject groups. It will be distributed to various groups upon request and can be further customized to meet their needs.

Advisory Committee

1) The Advisory Committee is scheduled to convene again on May 17, 1994. The second of the seminar series, "Risk Management" will be pilot-tested during the meeting. This course is an introduction to how risk concepts and theory impacts management decisions in regards to health and the environment. Committee members will be provided the opportunity to review course content, presentation, and materials through written and verbal evaluations.

Program Design and Development

1) Course development for the first Professional Development Seminar entitled "Concepts of Risk Analysis" is completed. This course is an introduction to the concept of risk, the risk assessment process (specifically for hazardous waste site remediation), and includes an introduction to risk management and risk communication.

   The course was pilot tested to the Advisory Committee November 3-5, 1993 in Charleston, SC. A second presentation of the course was also conducted in Charleston on February 1 and 2, 1994. Members of both EHAP, MUSC, and the Department of Energy, Savannah River Site attended the February seminar.

2) Literature searches are underway to obtain information for the development of the next two courses in the professional development series: Environmental Risk Management and Risk Communication.

   The Environmental Risk Management course is in the final stages of development.

Milestones and Deliverables Planned for Fourth Quarter

Planning/Administration

1) Networking & meetings planned for April - June, 1994.

   - TAPPI Research Management Committee, Department of Energy National Laboratory Tour; Westinghouse Savannah River Technology Center, Oak Ridge National Laboratory, Sandia National Laboratory, and Los Alamos National Laboratory, April 17 - 22, 1994. Committee member, Dr. Jan Temple.
   - Pilot test of second risk course, "Environmental Risk Management" May 18 - 19, 1994. Second pilot test of the course will occur at the end of June 1994.
   - Presentation of "Concepts of Risk Analysis" course at the Department of Energy Savannah River Site during May/June 1994.
   - Medical Curriculum Research Committee meeting. Dr. Jan Temple in cooperation with Dr. Catherine Musham and Jan Bellack will participate in meetings during the fourth quarter of fiscal year 1993.
   - Finalize Research Project with Ms. Lillian Mood, South Carolina Department of Health and Environmental Control, fourth quarter fiscal year 1993. Project

will address Risk Profiles for Environmental Quality Management, Health Professions, and Physicians.

- Development and delivery of courses on Risk Analysis, Toxicology, and Health Concerns of PCBs to the Charleston Naval Shipyard, Closure Engineering Division, during fourth quarter fiscal year 1993. The courses are part of an integrated development project between the Medical University of South Carolina, University of South Carolina, and Clemson University.

Needs Assessment Instrument

1) The revised needs assessment instrument that has been developed to better ascertain the level of risk awareness of subject groups. The instrument will be distributed to various groups upon request.

Advisory Committee

1) The advisory committee will hold a meeting May 17, 1994. Members of the committee will be invited to attend the initial pilot testing of the second Professional Development Seminar on Environmental Risk Management - May 18-19, 1994.

Program Design and Development

1) Course development for the first Professional Development Seminar entitled "Concepts of Risk Analysis" finalized.
   - Deliverables will include the agenda, student handbook, lesson plans, slides and other audio visual aids, course examination, and course evaluation.

2) Literature searches are underway to obtain information for the development of the next two courses in the professional development series: Environmental Risk Management and Risk Communication. The second course is scheduled to be pilot tested May 18-19, 1994.
   - Deliverables will include draft documentation from the Student textbook for the Environmental Risk Management course as well as a draft agenda.

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