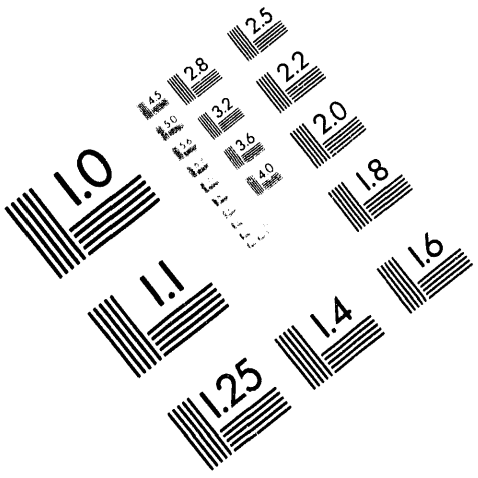
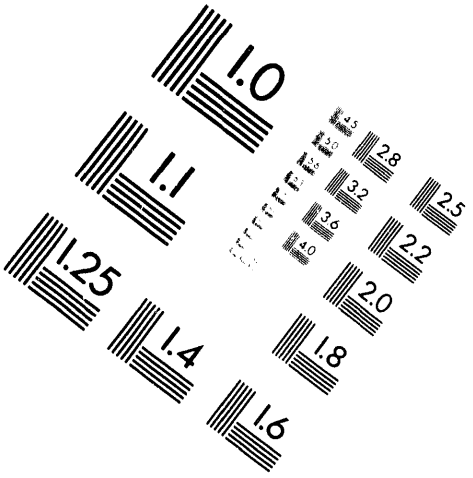
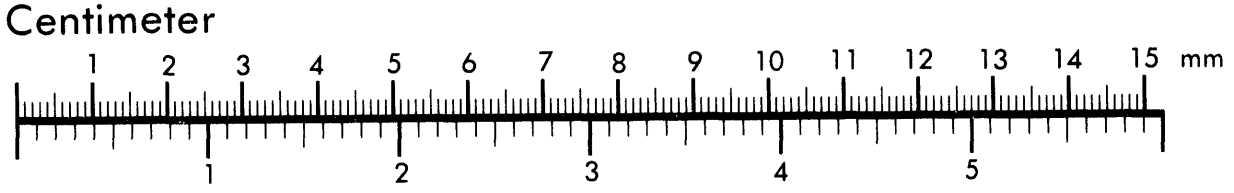
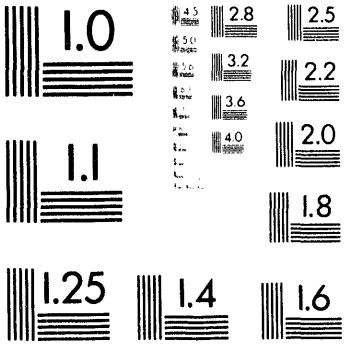
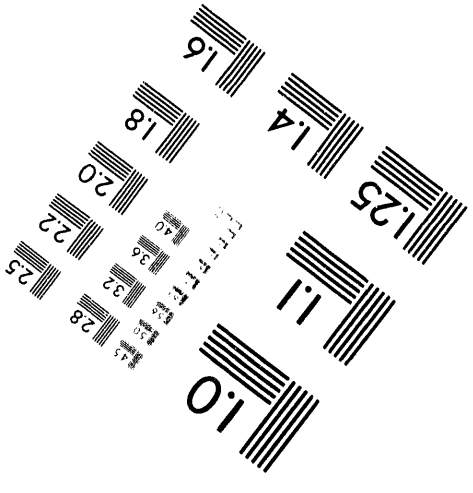


Association for Information and Image Management
1100 Wayne Avenue, Suite 1100
Silver Spring, Maryland 20910
301/587-8202









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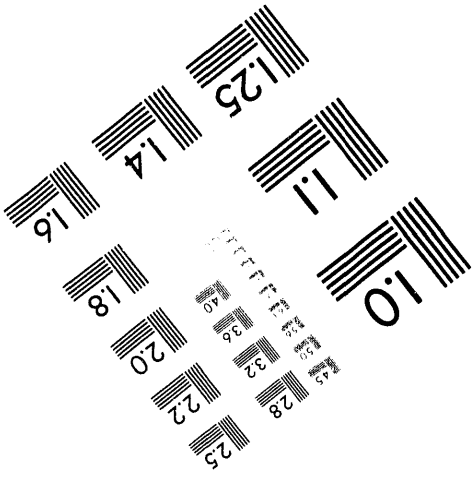

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DOE/EW/50625--T16

6/8-24-94

ENVIRONMENTAL HAZARDS ASSESSMENT PROGRAM
ANNUAL REPORT
July 1, 1993 - June 30, 1994

FOR

GRANT DE-FG01-92EW50625

SUBMITTED TO THE
U. S. DEPARTMENT OF ENERGY

BY THE

MEDICAL UNIVERSITY OF SOUTH CAROLINA

August 17, 1994

Table of Contents

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 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.

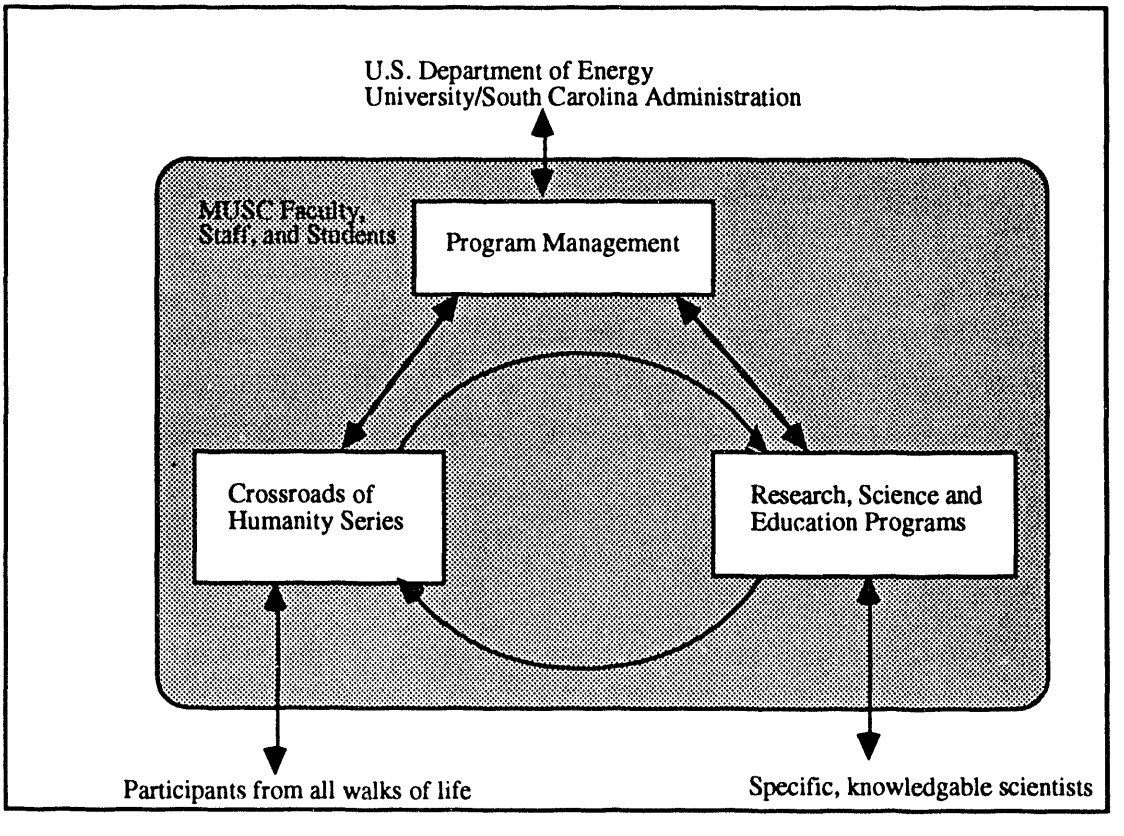


Figure 2.0. The Major Program Elements and Their Relationships.

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 Year 2 and total grant expenditures.

EHAP Year 2 and Total Expenditure Summary	Year 2	Total
	(Dollars in Thousands)	
Crossroads Series	1,356	2,202
Round Tables and Workshops		
Publications and Outreach		
Expert Support		
Research and Evaluation		
Research, Science & Education	3,163	4,409
Toxicology		
Risk Assessment		
Information Support		
Education and Training		
Indirect Costs	1,857	2,682
Equipment	559	929
Total	6,935	10,221

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
Director 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 and Deliverables Achieved - Year 2

(Note: The number in parenthesis after each deliverable in this report corresponds with the numerical sequence of deliverables in the notebooks provided under separate cover.)

1. The Grant Principal Investigator and the Director of EHAP announced the appointments of six members to the External Advisory Group (EAG) to be chaired by Dr. Frank Parker. The EAG's mission will be to review all grant activities and plans and provide guidance to the Principal Investigator. The broad background, demonstrated expertise and international reputation of our EAG members will provide us an invaluable critique of our programs. Such input will undoubtedly bring about significant improvements in focusing our research efforts so we can make the best possible use of the grant funding. We anticipate adding two additional members within the first quarter of year 3 at which time the first meeting and program review will be scheduled. The new members are:

   Frank Parker, Ph.D. (Chairman)
   Bernard D. Goldstein, M.D.
   Robert I. Hanfling
   Richard Meserve, Ph.D., JD

Glenn Paulson, Ph.D.
Ellen K. Silbergeld, Ph.D.

- External Advisory Group member biographies (1)

2. Negotiations between MUSC and Idaho National Engineering Laboratory (INEL) were completed with the signing of the Memorandum of Understanding (MOU) in the second quarter. The memorandum defines a working relationship which facilitates the development of collaborative efforts between MUSC and INEL. It is an important first step in establishing working relationships with other major research institutions.

   - Memorandum of Understanding dated November 17, 1993 (2)

   Subsequent to signing the MOU, efforts in the third and fourth quarters focused on developing formal collaborative programs in the areas of risk assessment and risk communication. Dr. Rosalie Crouch headed a seven-member team of MUSC scientists and researchers during a visit to INEL in the third quarter to advance this process. Further preliminary discussions were held between personnel at INEL and Dr. David Hoel to formulate risk assessment initiatives particularly in the area of bioremediation. A team from INEL visited Dr. Hoel's group in April to discuss the development of a scope of work for a collaborative risk assessment program involving INEL's Buried Waste Integrated Demonstration (BWID) and MUSC's Department of Biometry and Epidemiology.

   A second research cooperative program was initiated between INEL and MUSC when the manager of BWID attended the April Town Meeting with the purpose of modeling similar BWID community meetings after those developed in our Crossroads of Humanity Series. As a result, an agreement was reached to contract for EHAP to assist INEL with a public meeting regarding BWID. It is anticipated that the work will begin in the first quarter of year 3.

3. Similar dialog was begun in year 2 between MUSC and Brookhaven National Laboratory (BNL). Meetings between MUSC and BNL representatives took place in the first, second and third quarters for the purpose of establishing collaborative efforts between faculty of MUSC and staff of BNL. During the fourth quarter, it was agreed that, rather than pursue a formal MOU, we will work to establish collaborative research efforts and will formalize arrangements around specific programs.

4. MUSC and EHAP sponsored a national symposium on preventing child exposures to environmental hazards through the Children's Environmental Health Network held in Washington, D.C. during the third quarter.

5. A focus on environmental medicine in the development of a more credible method for establishing "health risk" associated with environmental hazards was initiated in the second quarter when Dr. Alan Ducatman, a highly regarded clinician in environmental medicine from the University of West Virginia, visited MUSC for discussions with Dr. Allen Smith and Dr. Stanley Schuman. The foundation for

this collaboration lies in the work already started at MUSC by Dr. Schuman as a part of this grant effort. In the third quarter, Dr. Smith secured a faculty appointment for Dr. Ducatman as an Adjunct Professor of Medicine at MUSC.

Dr. Ducatman, Dr. Smith and Dr. Schuman worked to develop new research initiatives combining traditional risk assessment with clinical methodologies to assess environmental hazards from a health perspective. Preliminary planning was begun in the third quarter to design, implement and evaluate a statewide approach to preparing physicians for their leadership roles in environmental health issues through statewide family medicine training systems and the MUSC Agromedicine program. They completed a videotape series entitled "Environmental Health for Physicians".

- Videotapes - "Environmental Health for Physicians" (3)

6. A research effort with AEA Technology Consultancy Services (AEA) to develop an overall framework for risk based decision making with respect to land use was contracted in the fourth quarter. The initiative was funded by the grant through MUSC's institutional technical support contract with Coleman Research Corporation. It is anticipated that once the framework is developed, it might be applied at nominated Federal facilities. EHAP's support of this project fits well with grant objectives in the areas of risk management and risk based decision making. In addition, MUSC is able to draw on the significant experience AEA brings to the table in addressing world-wide environmental problems. An interim progress report was delivered prior to June 30 to cover the first funding phase.

   - Interim Progress Report (4)

Milestones Planned for Year 3

1. The External Advisory Group will meet at in Year 3 to review all grant activities and programs and provide impartial, expert comments, advice and recommendations to the Principal Investigator and Director. It is expected that these in-depth evaluations will lead to significant improvements in focusing on the grant objectives as they have evolved over the past two years.

2. Two microbiologists will be hired in the first quarter to extend on-going research in the areas of dioxin and PCB's and to support the education initiatives in the new Masters in Environmental Studies jointly offered by MUSC and the University of Charleston.

3. The collaborative efforts between MUSC and INEL will continue to expand in Year 3. There are two specific areas with respect to INEL's Buried Waste Integrated Demonstration Project (BWID) which will be addressed early in Year 3.

   Professional Outreach and Public Involvement. Dr. Glenn Fleming and his staff will provide consulting services in panel formulation, selection, production and evaluation for public involvement forums. This collaborative effort is a direct outgrowth of the expertise developed by the Crossroads of Humanity Series

through its various roundtables, workshops and town meeting held in Years 1 and 2.

Risk Assessment. A MUSC team headed by Dr. David Hoel will continue preliminary discussions with INEL concerning risk assessment of BWID technology from a health perspective. Funding for this program will be resolved.

4. A cooperative effort among MUSC, DOE, the Air Force, TCE Issues Group, Cammer and Associates, Coleman Research Corporation and the ChemRisk Division of McLaren/Hart Environmental Engineering Corporation to produce an independent analysis for consideration in establishing safe clean-up levels of trichloroethylene (TCE) contaminated sites will be proposed for funding. It is expected that, should a proposal be accepted, considerable savings will be realized by the funding agency based upon close cooperation with grant-funded TCE research currently underway at MUSC.

5. Work begun in Year 2 by AEA Technology Consultancy Services (AEA) to develop an overall framework for risk-based decision making with respect to land use will be completed early in Year 3. AEA has significant experience world wide in addressing environmental risk assessment, risk management and risk communication issues.

6. Expanding the role of primary care physicians in the field of environmental medicine will be continued through the efforts of Dr. Allen Smith and Dr. Stanley Schuman. In addtion, an Associate Medical Director for the Occupational and Environmental Medicine Office (OEMO) will be named to assist in the design, implementation and evaluation of a statewide approach to preparing physicians for their leadership role in environmental health issues.

4.0 CROSSROADS OF HUMANITY SERIES

Director:	Glenn Fleming, Ed.D.
Research Director:	Catherine Musham, Ph.D.
Program Information Coordinator:	Richard Jablonski
Public Information Specialist (Publications):	Cathi Bare
Public Information Specialist (Database):	Jill Tompkins
Events Coordinator:	Sylvia Rivers
Research Associate:	Dylan Holmes
Administrative Assistant:	Percilla Coaxum
Temporary Student Assistant:	Kimberly Doctor

Year 2: A Brief Overview

During Year 2 (July 1, 1993 through June 30, 1994) the Crossroads of Humanity Series developed and implemented a wide range of programs, research and printed materials.

Efforts were consistent with achievement of EHAP's long-term objective: development of a holistic, national basis for risk assessment, risk management and risk communication, focused on human health.

During Year 2, the Crossroads Series addressed this objective in the following ways:

- Development and implementation of round table forums and workshops;
- Research in areas of risk perception and risk communication;
- Publication of printed materials related to EHAP and the Crossroads Series;
- Expansion and redesign of a database containing names, addresses and telephone numbers of individuals and organizations with expertise and/or interest in environmental issues;
- Development of sponsorship and co-sponsorship relationships with such organizations as the Idaho National Engineering Laboratory, the South Carolina Department of Health and Environmental Control (DHEC) and the Agency for Toxic Substances & Disease Registry (ATSDR); and
- Publication and information support of Program Management, Science, Education and Information Systems initiatives.

The Crossroads Series of Forums and Workshops

During Year 2, the Crossroads Series produced, sponsored or co-sponsored 12 programs. These included four multi-disciplinary, multi-issue workshops, a Socratic dialogue on environmental risk, a community meeting on environmental preparedness, and six other programs on such topics as immunogenetic risk assessment, risk perception and environmental equity.

Three Crossroads Series programs -- **In Search of Purity, Purity Revisited** and **Planning for Purity: a Community Meeting on Environmental Preparedness** -- aired on South Carolina Educational Television in April and May of 1994. Crossroads Series staff confirmed that the first two programs also appeared on KERA-TV in Dallas, TX; WPTO-TV in Dayton-Cincinnati, OH, and Kentucky Educational Television.

With their expert panels, live audiences, television viewership and videotape circulation, Crossroads Series programs contributed to EHAP efforts in the following ways:

- 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;
- Increased public awareness of environmental cleanup and management issues; and
- Increased public and professional perception of MUSC as a place where environmental issues are identified, discussed and resolved.

Publications

As EHAP and the Crossroads Series have grown, so has the program's demand for a variety of high-quality publications. During Year 2, Crossroads Series personnel conceived, designed and produced printed materials in support of:

- The development, execution and promotion of the Crossroads Series of round table forums and workshops;
- The development and promotion of MUSC's Ph.D. program in Environmental Risk Assessment and the MUSC/UoC masters program in Environmental Studies;
- MUSC/EHAP research; and
- EHAP in general (reports articles, newsletters, information sheets, etc.).

The Crossroads Series Database

From the program's beginning in June of 1992, EHAP has pursued contact and dialogue with experts in many environment-related fields. These experts may serve the program in a variety of ways, including participation in Crossroads Series events and providing suggested direction for EHAP.

For two years, EHAP has compiled a list of individuals and organizations capable of contributing to the program in these and other ways. For the purpose of maintaining contact with these people, EHAP created a database, including names, addresses and telephone numbers of experts and others. This database is a useful tool for mailing purposes, as well as maintaining more direct contact with specific people and organizations.

During the first two quarters of Year 2, the number of names and organizations contained in the Crossroads Series database increased substantially enough to warrant redesign of the database. That process was initiated during Quarter 3 and is ongoing.

At this time, the Crossroads Series database contains information on over 3000 individuals and organizations. More than 600 are designated as experts, panelists, or both.

Personnel
In order to meet the increasing demands of time and effort exacted by the growth of EHAP, the Crossroads Series staff grew substantially During Year 2.

Current personnnel added during Year 2 are: Sylvia Rivers (Events Coordinator), Jill Tompkins (Public Information Specialist), Dylan Holmes (Research Associate) and Kimberly Doctor (Temporary Student Assistant).

More additions are anticipated during Year 3.

Milestones and Deliverables from Year 2

4.1 Crossroads Research and Evaluation

1. Conducted literature review and compiled bibliography of risk communication research (ongoing).
2. Designed, planned and implemented surveys of patients at six family practice residency sites in order to understand more about patients' perceptions of environmental risks (study completed Quarter 1; data collected and compiled Quarter 2).
   - Preliminary Results to Family Practice Patient Environmental Risk Perception Survey (5)
3. Completed national surveys of three groups of medical educators: academic deans, family medicine residency program directors and nurse practitioner deans (Year 2, Quarters 1-2). Response rates were high (greater than 60 percent).
   Data analyzed and reports prepared for publication in scientific journals. Authors: Academic deans (Graber, Musham, Bellack, Holmes), family medicine residency program directors (Musham, Bellack, Graber, Holmes) and nurse practitioner program deans (Bellack, Musham, Graber, Holmes). (Quarters 3-4)
   - Results submitted for publication to the Journal of Family Medicine, Journal for Academic Research, and the Southern Nursing Research Society Ninth Annual Conference (6)
4. Collaborated with MUSC Department of Biometry and Epidemiology on telephone survey of residents of Savannah River Site to test hypothesis that concern about environmental hazards is a function of proximity of residence to the site (Quarter 1).
5. Conducted mail survey of pharmacists to assess the extent to which they are asked environmental risk questions by clients and their needs for environmental medicine education. Dr. Pat Meier (MUSC Department of Pharmacology) presented preliminary data before Society for Risk Analysis Convention, 12/6/93 in Savannah, GA.
6. Developed survey instruments for Crossroads of Humanity Series workshop evaluations (Quarters 1-2).
   - Crossroads of Humanity Workshop Evaluations (7)
   - August, September, October 1993, summary results compiled and analyzed. February 1994 evaluation. April open-ended responses (8)
7. Continued a qualitative study of language used by lay people in discussing environmental issues for the purpose of developing easily understood information materials for the general public.

8. 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 (Quarter 3). David Graber completed preparation for poster presentation on the results of the medical educator survey accepted for presentation at the same symposium (Quarter 4).
    - Abstract: Educator's Views on Ecosystem and Environmental Content in Health Professions Education (Authors: David R. Graber, M.P.H., Ph.D., Catherine Musham, Ph.D., Jan Bellack, Ph.D.) (9)
9. 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).
10. Planned to pilot a study of lead poisoning education materials in the low income/minority community of Charleston (Quarters 3-4) Will be working with with members of the Charleston Childhood Lead Program. Six focus groups will be conducted in late July, 1994.
11. Designed survey instrument for a mail survey of occupational/environmental nurses in conjunction with the College of Nursing at MUSC (Quarter 4). This study will measure nurses' attitudes toward an environmental health nursing graduate program presently being developed at the College of Nursing.
    - Environmental and Occupational Health Nursing Survey. (Year 3, Quarter 1) (10)
    - Purposal for Graduate Environmental/Occupational Health Nursing Courses (11)
12. Planned a conglomerated study comparing the results from the studies listed above. Plan to submit the conglomerated paper for publication August, 1994.
13 Formed a new research group focusing on study of environmental health education for nurses and other medical professionals. Participants include Jan Bellack, Ph.D., Jan Temple, Ph. D., Dylan Holmes, Elizabeth Erkle, Ph.D.
14. Planned continued study of lay people's language pertaining to environmental risks and issues in additional focus groups.
15. Conducted two focus groups of people who attended EHAP's Community Meeting on Environmental Preparedness (5/94)
    - Focus group report (12)
16. Attended the following professional seminars, conferences and meetings:

    Seminar entitled Concepts of Risk Analysis, Feb 1-2, 1994, in Charleston, SC.

    Conference entitled Health Research and the Need to Ensure Environmental Justice, Feb. 10-12, in Washington, DC.

    EHAP's Perceived Risk Advisory Committee Meeting, Feb. 24-26, 1994, in Charleston, SC. Planned collaboration on Savannah River Site and other studies.

    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 (Quarters 3-4).

People and the Planet, sponsored in part by the University of South Carolina Center for Environmental policy, Institute for Public Affairs, April 15, 1994, Columbia, SC.

Monthly meetings of the South Carolina Family Practice Research Consortium to obtain support for environmental risk perception and communication research.

- Meeting notes, March 16, 1994, including copy of proposed Norplant Removal study in teens, submitted by Catherine Musham (13)
- Meeting notes, May 18, 1994 (14)
- Meeting notes, June 15, 1994 (15)

One-day seminar in "Risk Communication" conducted by Max Lum, ATSDR

Drs. John Dunbar and Glenn Fleming to conceptualize a study of environmental risk-related attitudes and effects of education in the community of Blackville, SC (Quarter 4).

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. (Technical assistance provided by research associate Dylan Holmes).

4.2 Workshops and Forums

1. Continued Crossroads of Humanity Series of workshop and forums, producing and/or sponsoring 12 programs during Year 2 (7/93-6/94).
These programs employed a variety of formats and included numerous co-sponsors. Formats included a socratic dialogue, multi-disciplinary and multi-issue workshops, single-discipline workshops, single-issue workshops and a community meeting. Sponsors included DHEC, ATSDR, the Center for the New West, the Harmony Institute, the MUSC College of Nursing, and the Children's Environmental Health Network.
Titles of these programs were:

Crossroads Series Workshop I - July 18-20, 1993 (16)

- Workshop I notebook
- Workshop I notes
- Workshop I brochure

Crossroads Series Workshop II - August 22-24, 1993 (17)

- Workshop II notebook
- Workshop II notes
- Workshop II brochure

Crossroads Series Workshop III - September 26-28, 1993 (18)

- Workshop III notebook
- Workshop III notes
- Workshop III brochure

Crossroads Series Workshop IV - October 24-26, 1993 (19)

- Workshop IV notebook
- Workshop IV notes

- Workshop IV brochure

Purity Revisited: A Socratic Dialogue on Environmental Risk - November 13, 1993 (20)

- Purity Revisited brochure
- Purity Revisited poster
- Purity Revisited videotape

Perceived Risk Advisory Committee - February 24-26, Charleston, SC (21)

- Perceived Risk Advisory Commitee Meeting Notes
- Perceived Risk Advisory Commitee program

International Conference on Immunogenetic Risk Assessment in Human Disease March 6-8, 1994, Charleston, SC (22)

- International Conference program
- International Conference registration Form
- International Conference poster

Preventing Child Exposures to Environmental Hazards: Research and Policy Issues (March 18-19, 1994, Arlington, VA)

Planning for Purity: A Community Meeting on Environmental Preparedness - April 23, 1994, Charleston, SC (23)

- Planning for Purity brochure
- Planning for Purity reminder postcard
- Planning for Purity videotape
- Planning for Purity poster
- Planning for Purity press kit

The Harmony Institute on Environmental Compatibility - April 28-30, 1994, Charleston, SC

- Harmony Institute report (24)

The Quiet Revolution: New Grassrooots Coalitions in Natural Resource Decision-Making (May 25-26, 1994, Denver, CO)

Clues to Unraveling the Association Between Illness and Environmental Exposure June 3, 1994, Charleston, SC (25)

- Clues program and registration form
- Clues report

2. Reviewed Workshop I-IV tapes for materials appropriate for brief, single-issue tapes (Quarters 3-4). Planned editing and production of first Workshop Instructional videotape to take place during Year 3, Quarters 1-2.
3. Planned issue- and discipline-specific workshops. Met with Mount Pleasant, SC, Mayor Cheryll Woods-Flowers to discuss concept (Quarter 4). Plan to convene first discipline-specific workshop Year 3, Quarter 2.
4. Met with representatives of Idaho National Engineering Laboratory (INEL) for purpose of discussing proposed community meeting in Idaho Falls, ID (Quarter 4). Will meet again Year 3, Quarters 1-2. Proposed meeting date: Year 3, Quarter 2.
5. Met with representatives of Blackville, SC, for purpose of discussing EHAP-related outreach activities in that town (Quarter 4). Will meet again Year 3, Quarters 1-2.
6. Met with representatives of Albright & Wilson Company of North Charleston, SC, for the purpose of discussing EHAP-related activities affecting that company surrounding neighborhoods (Quarter 4) Will meet again Year 3, Quarters 1-2

7. Attended National Association of Environmental Professionals Annual Meeting, June 14-18, 1994, New Orleans, LA.
   - Report (26)

4.3 Publications/Information

1. EHAP general information brochure (November, 1993)
   - Brochure (27)
2. Designed, published and circulated EHAP News & Information Newsletter. Circulation approximately 1500 (28)
   - Newsletter (July-August, 1993)
   - Newsletter (November-December, 1993)
   - Newsletter (January-February, 1994)
3. Designed, published and circulated Crossroads Update (29)
   - Crossroads Update (July, 1993)
   - Crossroads Update (August, 1993)
   - Crossroads Update (September, 1993)
   - Crosroads Update (October, 1993)
4. Designed, published and circulated EHAP Fact Sheets (30)
   - Fact Sheet (September, 1993)
   - Fact Sheet (December, 1993)
   - Fact Sheet (December, 1993)
   - Fact Sheet (December, 1993)
   - Fact Sheet (December, 1993)
   - Fact Sheet (April, 1994)
5. Published brochures for the Medical University of South Carolina's doctoral-level program in Risk Assessment and masters-level program in Environmental Sciences. Designed and published Ph.D. program poster. (31)
   - Ph.D. brochure
   - Masters brochure
   - Ph.D. poster
6. Prepared exhibit materials for participation in DOE Environmental Restoration and Waste Management Innovative Technology Development Progress Through Partnership Exhibit (December, 1993).
7. Directed a study to evaluate the environmental health supports needs of small towns and what MUSC/EHAP can do to address those needs.
   - Small Town Environmental Health (32)

4.4 Expert Support

1. Continued Crossroads of Humanity Series of forums and workshops.
   During Year 2, the Crossroads Series produced and/or sponsored 12 programs, including two round table forums. One important product of these programs is lists of individuals and groups interested in environmental issues. During Year 2, the total number of entries in the Crossroads Series database increased to 3000, with 600 of those designated as "experts."
2. Continued major overhaul of Crossroads of Humanity database, adding experts as they were identified/recruited and deleting those experts who have expressed no interest in EHAP (Quarters 1-4). Due to increased demands on the Crossroads

database, new software is being investigated, with the goal of a changeover during
- Year 3, Quarter 1.

Milestones Planned for Year 3

The Public and Professional Involvement program of the Environmental Hazards Assessment Program (EHAP) has emerged to be a program about "process".

In years one and two, the activities of the EHAP Crossroads Series, including the forums and workshops, have demonstrated that the national crisis of society's inability to translate clean-up and remediation policy into action in the area of environmental hazards management, the lack of understanding on the part of health care practitioners of environmental risk as a health factor, and the failure of professional and elected officials to accept broader leadership roles in resolving risk decisions is the failure of the "process" not of technology or of the science that is available.

As a result of their participation in the EHAP Crossroads forums and workshops, the participants cited the following factors as the basis for our inability to reach the action stage in resolving environmental risk conflicts.

- The public's inability to resolve conflicting information from equally credible resources.
- The public's perceived lack of influence over local cleanup decisions.
- The public's failure to understand or their unwillingness to accept the economic tradeoffs necessitated by the cleanup process.
- Inexperienced, uninformed or uninspired leadership
- Insufficient planning in the community for environmental-related incidents.
- Poor communication between affected parties.
- Lack of trust and
- Lack of knowledge of the "process".

Understanding this, the proposed program for EHAP Public and Professional Involvement activities for Year 3 is primarily concentrated on activities and research in the community. It is our goal to document, and validate, our assumptions about what can be done to develop the ability of communities, as well as individual members, to make decisions and react constructively to situations involving environmental incidents.

I. Community Development

In Year 3, EHAP Public and Professional Involvement Programs will address the issues of community participation in the process of understanding and acting upon environmental risk issues in community settings.

As an extension of our Crossroads activity we will begin to test whether or not a designed intervention can bring communities (this includes discipline specific groups such as nurses, dentists, lawyers, etc.) to the point where they can and will make decisions about the environmental health risks in their community.

A major part of the community development component will be the research documentation of the community's activity.

As directed by the work of the EHAP Crossroads workshop and forum panelists and participants during Years 1 and 2, , we will target three representative communities:

1. **An unincorporated rural area.**
The community we have selected for this is Cassatt, SC.

Program objective: Through a collaboration with the State Department of Health and Environmental Control, the College of Public Health at the University of South Carolina (USC), the College of Nursing at USC, and the MUSC College of Medicine our objective is to:

a assist the community with a health assessment
b develop a process for influencing the decisions that are made regarding environmental health risk in the community,
c be a source of un-biased, dependable information.
d apply the lessons learned from the Crossroads programs to the development of the community.

- document and report these activities in appropriate formats.

2. **An incorporated small community.**
The town of Blackville, SC has been selected as the setting of this project.

Program objective: Working with members of the community, we will design and implement a program which will:

a assist the community in developing a broadened perspective of the environmental health risks in the community.
b develop mechanisms which will facilitate the exchange of information within the community.
c allow the citizens to develop their agenda for which problems should be addressed and how.
d begin to develop a process in the community which will allow the citizens to feel that they can influence the resolution of these problems.
e apply the lessons learned from the Crossroads programs to the development of the community.

- document and report these activities in appropriate formats.

3. **An urban/industrialized community.**
Plans have not been finalized at this time, however, negotiations are underway to work with an industrialized section of Charleston, SC referred to as "the Neck".

Program objective: Working with members of the community, the College of Medicine at MUSC, the State Department of Health and Environmental Control,

- the Environmental Protect ion Agency, and targeted industry, we will develop a program which will:
    - a assist the community in developing a broadened perspective of the environmental health risks in the community.
    - b develop mechanisms which will facilitate the exchange of information within the community.
    - c allow the citizens to develop their agenda for which problems should be addressed and how.
    - d begin to develop a process in the community which will allow the citizens to feel that they can influence the resolution of these problems.
    - e apply the lessons learned from the Crossroads programs to the development of the community.

- document and report these activities in appropriate formats.

II. Crossroads Workshops and Forums

Discipline and Issue Specific Forums

4. Issue specific workshop/forum: Current risk assessment practice redefined to meet community physician's needs.
   Coordinators: Dr. W.A.Smith and Dr. Alan Ducatman

5. Issue Specific workshop: Small community mayor's guide to leadership in the midst of an environmental incident.
   Coordinators: R. Jablonski, EHAP, Honorable Cheryl Woods-Flowers, Mayor, Town of Mt. Pleasant, SC

6. Discipline Specific workshop: The dentist's need for environmental health issues information
   Coordinators: Dr. R.A. Draughn and Dr. Allen Smith

Programs for which no coordinators have been designated include:

7. A discipline specific workshop for the legal profession to describe, "How it should be" in legal matters relating to environmental risk.

8. A follow-up discipline specific workshop for nurses/nurse practitioners on environmental health risk. (first was held in 1994.)

III. Risk Communication Research

Studies which are designed, and will be conducted in Year 3 include:

9. The family physicians perceptions of communication of environmental risk as opposed to life style risks.

10. Community perception of lead poisoning education programs.

11. The nurse practitioners perception of the need for environmental health information.
    for the practitioner
    in the educational program

12. Environmental health for General Dentistry Residents. Following a survey of dentists to establish need, a course for general dentistry residents will be developed at MUSC.

5.0 RESEARCH, SCIENCE AND EDUCATION

5.1 Toxicology Projects

5.1.1 Immunological Consequences of Beryllium Exposure

Project Director:	Jean-Michel Goust, M.D.
Co-Investigator:	Philippe Arnaud, M.D., Ph.D.
Research Technician:	Clay C. Dannenhower

INTRODUCTION & BACKGROUND.

The possible health effects of beryllium are of emerging concern, particularly under circumstances where exposure may be intermittently or continually high. Beryllium is used in the nuclear and the lighting industries. It is responsible for a chronic respiratory disease progressing to respiratory insufficiency in a small percentage of individuals exposed to it by inhalation. Two apparently distinct patterns of pulmonary disease may be observed. Acute pneumonitis and chronic interstitial beryllium disease, which *appears to* represent a hypersensitivity reaction. The mechanisms underlying Chronic Beryllium Disease (***CBD***) are poorly understood but the lung pathologies of ***CBD*** and ***Sarcoidosis*** are identical. Both are characterized by the existence of a chronic lung granuloma formed by activated T cells surrounding giant cells derived from alveolar macrophages. Some progress has been made in elucidating the mechanism of beryllium-induced disease. Inhalation, and especially that of particles of a certain critical size range, appears to provoke inflammatory responses and attempted ingestion by alveolar macrophages. However, in the chronic form, alveolitis with mononuclear infiltrates and formation of non-caseating granulomas are prominent features, suggesting that beryllium can elicit a specific immune response, compartmentalized into the lung (1-3). These T cells are of the CD4 phenotype and restricted by class II HLA molecules. They respond only to beryllium and not to any other metal, establishing the specificity of the response (4). However, if ***CBD*** is an autoimmune response where beryllium plays the role of an antigen, the most likely sequence of events is as follows: inhaled beryllium enters normal alveolar macrophages which can retain beryllium for months or years. In these cells, beryllium may associate with endogenous peptide*(s)* normally expressed by alveolar macrophages. Subsequently, this beryllium-modified peptide becomes associated with the HLA-class-II molecules and would be expressed at high levels by alveolar macrophages.(5, 6) In mice, only those possessing the $H2^k$ phenotype develop a similar disease (7). This restriction to only one MHC haplotype suggests an important role played by class-II MHC molecules in this model. A similar observation has recently been made in human CBD, where alleles of the DPB1 class can confer resistance or susceptibility(8). These particular class II alleles in CBD could affect the interactions between the immunogenic peptides and the class-II molecule (9).

Our hypothesis is that Be^{2+} binding through its positive charges to a set of 2 or 3 negatively charged residues in the DPB1 chain, will interfere with the binding of normal peptides to the DP molecule. These residues appear to be critically

important for the binding of normal peptides. Be^{2+} binding to only one residue in region C or two in region D would not be enough to significantly alter peptide binding.

Objectives:

To isolate the MHC-bound peptides present in the murine IA^k and IE^k molecules and to the human HLA DP molecules associated with susceptibility and resistance to Beryllium disease and to compare their structure.

To demonstrate that Beryllium modifies the binding parameters of these peptides to the MHC molecules.

Milestones Achieved in Year 2

1. To produce MHC molecules of the different types by using human and murine individual cell lines homozygous for the MHC type of interest.

   We have obtained the murine CH-1 cell line producing specific MHC molecules (I-A^k and I-E^k) and we have increased the production to $6x10^9$ cells/wk. A total of $5x10^{10}$ cells have been produced.

   We have purified the membranes of these cells and demonstrated both by immunofluorescence and SDS-gel electrophoresis that they express the desired MHC molecules.

2. To produce monoclonal antibodies which recognize the above molecules and to purify them.

   We have produced monoclonal antibodies to I-A^k and I-E^k molecules and purified them by affinity chromatography on Protein-A Sepharose. So far, 25 mg of anti-I-Ak have been purified (out of 25 L of cell culture, and the amount of I-Ek exceeds this number. The purity of these antibodies is excellent, as judged by SDS-PAGE, and their activity is fully conserved (see above).

   We have obtained in June 1994 the cell lines producing monoclonal antibodies to human DP molecules (from Dr. G.B, Ferrara, Genova, Italy) and the DP- and DR-expressing cell lines, and we have begun to grow them. We will follow the same protocol as above for theantibody purification, except that they will be purified on Protein-G Sepharose. When enough material is isolated, new affinity columns will be built and used for DR subtraction and DP purification.

3. To improve our methods using insect cell cultures, we have produced a human plasma protein in this system, which represents a system somewhat simpler than the one that we intend to use for MHC molecules. The production has been very successful, and we feel confident that we can now (Jan-Feb 1995) produce the two alpha and beta chains of specific DP phenotypes.

- Abstract - "Human Recombinant Alpha2-HW Glycoprotein-Fetuin-pp63 is an Inhibitor of the Insulin Receptor Tyrosine Kinase. FEBS Letters (submitted August, 1994) (33)

Milestones Planned for Year 3

4. To bind these antibodies to N-Hydrosuccinimide-activated Superose columns.

   We are in the process of binding the anti-I-A^k and anti-I-E^k antibodies to the affinity column. A special program of ligand recycling has been set for this purpose with the help of Pharmacia.

5. To purify these MHC molecules by affinity chromatography using the above monoclonal antibody columns.

6. To isolate the endogenous peptides bound to these MHC molecules by molecular sieving and to compare their structure as determined by tandem mass spectrometry.

   The affinity columns anti I-Ak and I-Ek will be ready to work before the end of August. The purification of the MHC molecules will then begin, and substantial amounts should be obtained soon (September 1994). The isolation of the peptides by molecular sieving and their delivery to Dr. Dan Knapp for sequence by tandem mass spectrometry will follow (probably in October 1994).

7. To synthesize in insect cells and purify recombinant MHC molecules of the desired phenotype using the recombinant baculovirus system and to study their binding to specific peptides from phenotypes conferring either resistance or susceptibility to Beryllium disease.

   We have obtained the sequence of the MHC molecules of interest and plan to express them in insect cells using the recombinant baculovirus system (14). To do so, we have worked out several conditions which are critical for our purpose, including design of primers, increase of recombinants, large-scale production of proteins by insect cells and purification using Histidine tags. We project to begin the production in early 1995.

Miscellaneous:

A NIEHS conference on Beryllium disease is to be held November 17-19, 1994, the proceedings of which will be published soon after in Archives of Environmental Health. Our Laboratory will participate to this meeting and present our state of achievement.

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
Laboratory Technician:	P. Werner

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 1 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 α and β (chromosome 6), T cell receptor α and Gm (chromosome 14), and Km and interleukin-1β (chromosome 2). Both serological and molecular methodologies will be employed to study the distribution of these genetic markers.

Objective 2 To examine TNFα and IL-1β 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-1β gene expression will be studied.

Completed 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 scrum DNA: (6/94)

7. Characterization of TNF and IL-1 probes: (12/93)

8. Examination of expression of TNFα and IL-1β in activated monocytic cells, by Northern and slot blot hybridization studies : (6/94)

Milestones and Deliverables Achieved:

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 TNFα is being expanded, purified, and labeled with biotin. Similarly, biotin labeled probes for human IL-1β are being prepared from pBluescript plasmid containing a cDNA for IL-1β.

   Characterization of TNF and IL-1 probes: 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 electrophoresis 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 TNFα and IL-1β, 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 TNFα 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 TNFα mRNA, and that this effect is enhanced by the presence of fluoride ions. ELISAs for quantitation of TNFα and IL-1β in the culture media of these experiments showed release of both cytokines. (9/93)

Characterization of the TNF-α 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-α 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 stretch of DNA in the class III region of HLA on chromosome 6. TNF-α is important in several immunological activities and is a central mediator of the inflammatory responses. It has been speculated that in many HLA-associated diseases the primary association may be with the TNF-α alleles. The newly described biallelic polymorphism in the promotor region of the TNF-α is ideal for such studies. Patients with CBD will be characterized for this genetic marker.

   Study of TNFα polymorphism by PCR: We can now determine all known alleles of the TNFα locus by the PCR methods. This will add to our 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-α alleles. The results showed that the distribution of the three genotypes was similar in both groups. (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-α 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 (3/94).

5. The newly described biallelic polymorphism of the TNF-α 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-α.

   Expanded studies of TNF-α alleles and cytokine production in our control population have been performed (3/94).

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 (3/94).

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 (3/94).

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 has been performed on samples from Dr. Newman. (We have not as yet received genomic DNA from Dr. Saltini). (4/94).

   Serologic determination of Gm and Km allotypes will be performed on serum samples (5/94).

9. Genotyping by PCR using serum

   A large, previously HLA typed control population has been characterized with respect to the TNF-α alleles by PCR (6/94).

Milestones Planned for Year 3:

1. We have allotyped silicosis patients, and are awaiting blood samples from subjects who have been exposed to silica dust but remain healthy (controls). These samples will be similarly typed.

   - Statistical analysis of Ig allotypes and silicosis data

2. Preliminary studies of Ig allotypes have been performed on a limited number of serum samples from patients with berylliosis. Additional sera and DNA are expected to arrive shortly from Dr. Saltini, and will be similarly characterized.

   - Statistical analysis of Ig allotypes and berylliosis data

3. Initial studies have established conditions for determination of TNF-α allotypes in two polymorphic systems by PCR RFLP, and a number of healthy control subjects have been characterized. Additional patient and control material will be analyzed as it becomes available.

   - Characterization of TNF-α alleles in patient and control DNA

4. The methodology for determination of IL-1β allotypes by PCR RFLP has also been established, and a number of healthy control subjects have been characterized. Additional patient and control material will be analyzed as it becomes available.

   - Characterization of IL-1β alleles in patient and control DNA

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.

Project Description:

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.

Background

1,1,2-Trichloroethylene (TCE) is a commonly used industrial solvent that has become a common environmental contaminant. At DOE sites it is the most abundant chlorinated hydrocarbon contaminant, being present in groundwater 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 has also been associated with a life-threatening systemic scleroderma-like disease. This condition has reported to have occured following occupational exposure, and from drinking water contaminated with TCE. It is hypothesized that covalent binding of TCE reactive metabolites to certain (unknown) proteins may initiate this autoimmune disease.

Covalent binding to protein has also received considerable attention as a possible internal dosimeter (i.e., biomarkers of exposure). Measurement of covalent binding to protein 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" (i.e., the concentration of a toxic metabolite at its site of action within specific cells or tissues) 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 covalent binding of TCE metabolites to 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. We will also synthesize putative TCE-protein adducts for use as immunogens to raise antibodies against 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 other hazardous waste sites.

Results and Discussion:

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

1. Separation and analysis of unmodified and TCE-modified human hemoglobin α and β chains. Human hemoglobin was incubated in phosphate buffer (pH 7.4) alone, or buffer containing the TCE reactive metabolite dichloroacetyl chloride (or

dichloroacetic anhydride, 15 mM). The hemoglobin samples were then dialyzed under pressure against ammonium acetate buffer (50 mM, pH 8.0), and lyophilized. The samples were then redissolved and analyzed by high performance liquid chromatography (HPLC) and mass spectroscopy (MS). Figure 1 shows HPLC chromatograms of unmodified and dichloroacetyl chloride-modified hemoglobins, which were separated into their components (heme, a and b chains) on a reversed-phase C-4 column. No difference was observed between unmodified and modified hemoglobin a and b chains in regard to retention times or in the appearance of the two peaks.

- Figure 1

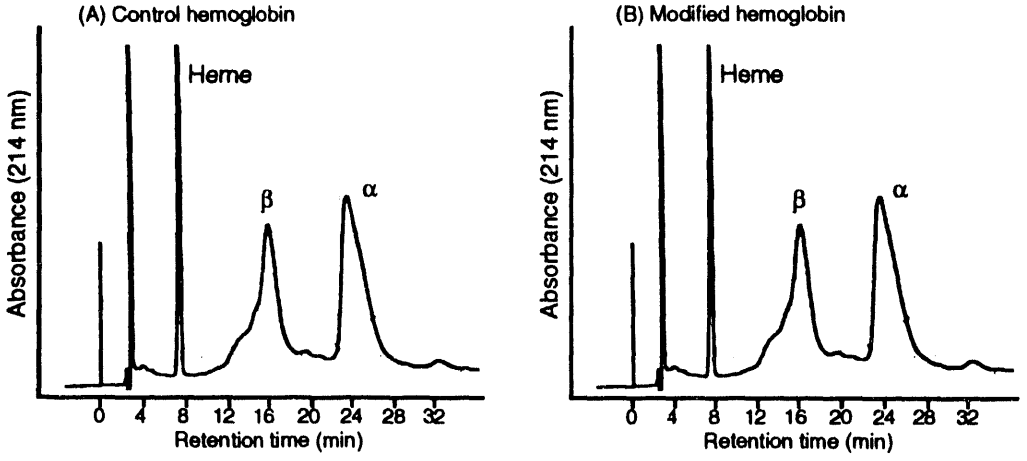
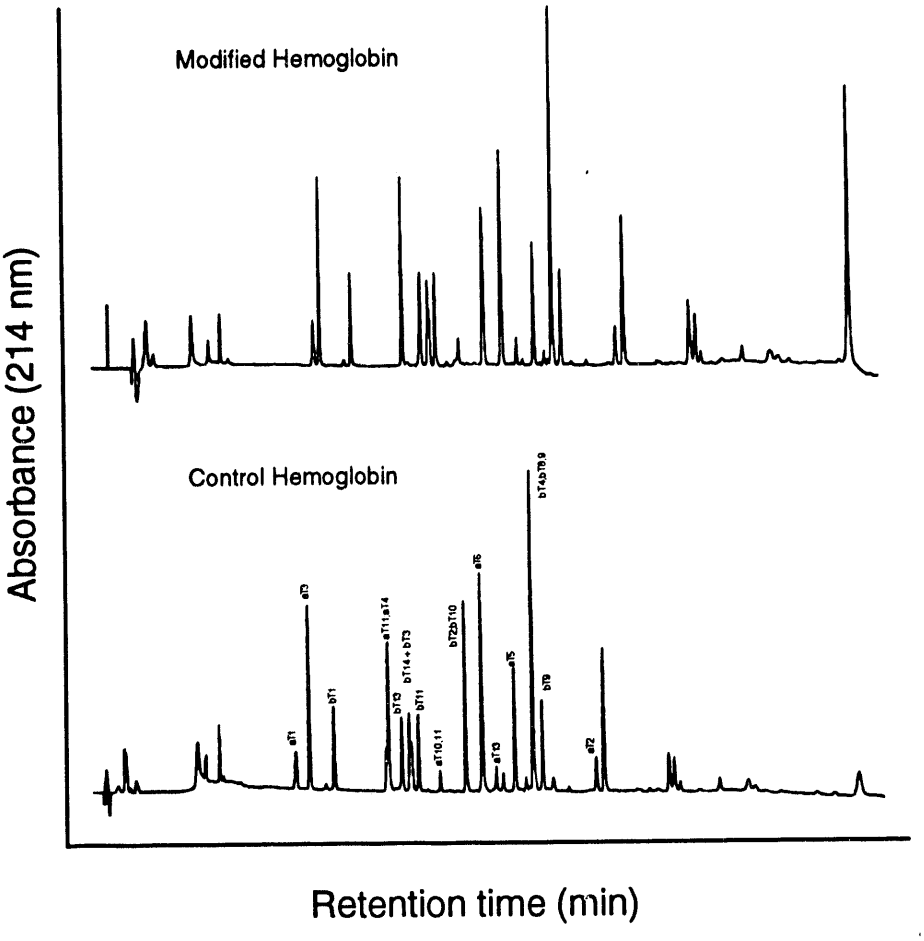


Figure 1. HPLC chromatogram of (A) human hemoglobin and (B) human hemoglobin modified with dichloroacetic anhydride (15 mM). Hemoglobin a and b chains were separated on a Brownlee C-4 reversed-phase column, and were eluted with a linear gradient of 44% solvent A (aqueous 0.1% TFA) to 57% solvent B (0.084% TFA in acetonitrile) in 60 min at 1 ml/min.

Mass spectral analysis of human hemoglobin α and β chains. Hemoglobin a and b chains were purified by HPLC, and then subjected to MS analysis (data not shown). The molecular weights that were observed for unmodified a (15,128) and b (15,846) chains were similar to those reported previously by other investigators. No difference in molecular weight was observed between unmodified and modified hemoglobin a and b chains.

2. Tryptic digestion of unmodified and TCE-modified human hemoglobin. Human hemoglobin samples (unmodified and modified) were digested into peptide fragments by the protease trypsin, which cleaves after lysine and arginine residues. Tryptic peptides were then separated on a C-18 reversed-phase HPLC column, and the results are shown in Figure 2. Tryptic fragments were then identified by mass spectroscopy (see below). No difference was observed in the HPLC profiles of unmodified and modified hemoglobin.

- Figure 2



Mass spectral analysis of human hemoglobin tryptic peptides. The tryptic peptides described above were purified by HPLC, and analyzed by MS. All of the "observable" tryptic fragments of both a and b chains were resolved, including several incomplete digestion fragments. Figure 3 shows representative spectra of the same peaks isolated from unmodified and modified hemoglobin. No difference in the molecular weight of tryptic fragments from unmodified and modified hemoglobin were observed.

- Figure 3

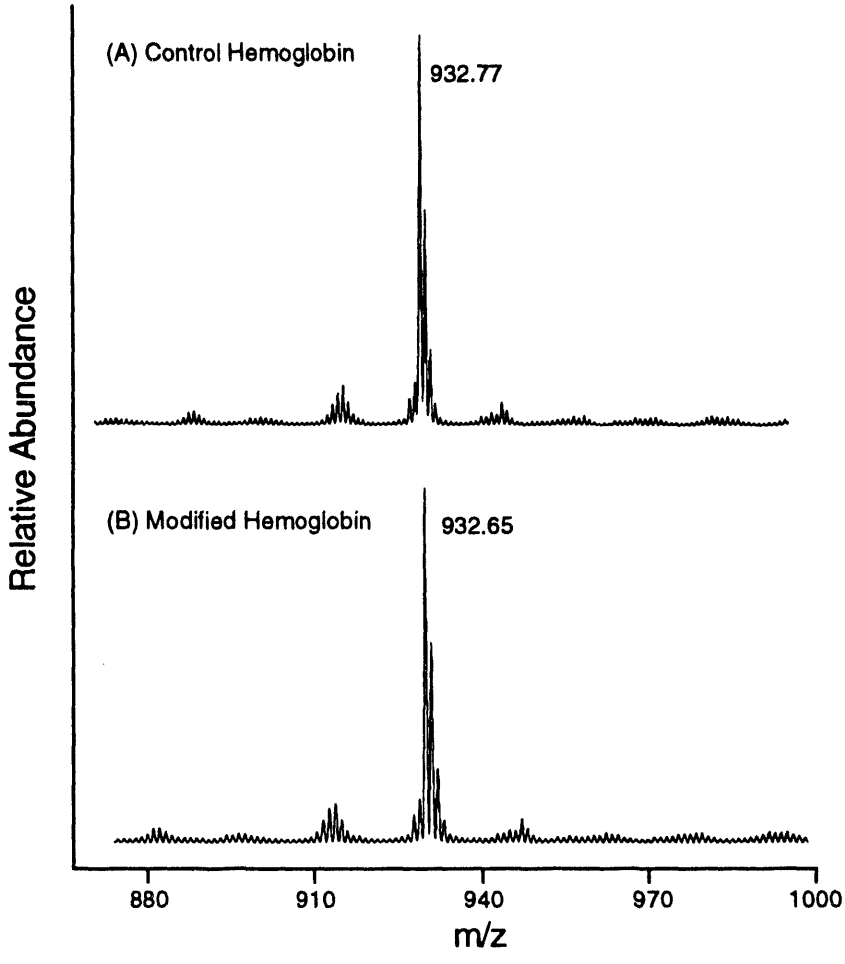


Figure 3. Mass spectrum of human hemglobin tryptic peptide fragment βT2 (9-17) from (A) human hemoglobin and (B) dichloroacetic anhydride-treated human hemoglobin. Tryptic fragments were purified by HPLC prior to mass spectral analysis.

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

Milestones and Deliverables Achieved

1. Immunogen preparation and antisera collection. Dichloroacetyl chloride (15 mM) was incubated with the immunogenic carrier protein, keyhole limpet hemocyanin (KLH), in a manner analogous to the reaction described above for modification of human hemoglobin. Modified KLH was then dialyzed against buffered saline, and injected subcutaneously and intramuscularly into rabbits. The immunogen was readministered again after two weeks, followed by collection of blood samples (~10 ml). The blood was centrifuged, and the antibody-containing serum was collected, and frozen at -70°C.

2. Detection of TCE adducts *in vitro*. Unmodified hemoglobin, and hemoglobin modified with dichloroacetyl chloride, were examined by ELISA for the presence of TCE adducts using anti-TCE antibodies. Although no evidence for adduct formation was observed using HPLC and MS analysis (see above), use of anti-TCE antibodies in an ELISA detected the presence of very low levels of TCE adducts (data not shown).

3. Synthesis of anti-TCE antibody inhibitors. In order to synthesize an inhibitor for antibody specificity characterization (in a competetive ELISA), Z-lysine was derivatized overnight with dichloroactic anhydride in chloroform. The resulting dichloroacetylated Z-lysine was then deblocked in trifluoroacetic acid, and recrystallized from chloroform. The identity of the product was confirmed using MS and NMR.

Non-competetive enzyme-linked immunosobent assay (ELISA). A test antigen was prepared by reacting dichloroacetyl chloride with rabbit serum albumin, in a manner analogous to that described above for modification of KLH. This test antigen was then applied to the bottom of 96-well plates, and dried. Diluted serum from rabbits immunized with modified KLH was then added to the plates containing the test antigen, and allowed to incubate for 2 hr. The serum was washed out, and a secondary (detector) antibody (goat anti-rabbit IgG conjugated with alkaline phosphatase) was added to the plates. After washing, the relative amount of antibody was determined by addition of the substrate to the bound secodary antigen, and the results are shown in Figure 4. These data indicate the presence of a high titer of antibodies against TCE bound covalently to protein.

- Figure 4

Detection of TCE adducts *in vivo*. In a separate experiment, mice were given an intraperitoneal injection of TCE dissolved in corn oil (1000 mg/kg). Three hours after administration, the animals were sacrificed, and the livers were removed and homogenized. Cytosolic liver protein was separated by acrylamide gel electrophoresis, and the proteins were blotted onto nitrocellulose. The blot was then immunostained using anti-TCE antibodies, and the results are shown in Figure 5. A number of protein bands containing TCE adducts were detected. The majority of covalent binding was to a protein of approximately 67 kDa, which corresponds to the molecular weight of albumin. Higher molecular weight protein adducts, possibly cross-linked proteins, were also observed.

- Figure 5

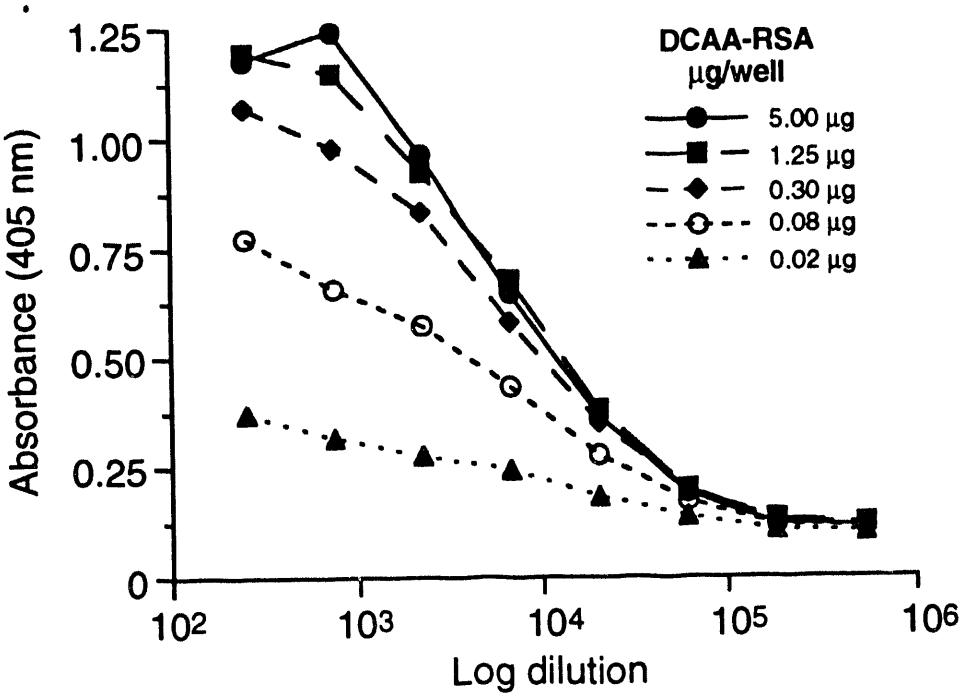


Figure 4. Noncompetetive enzyme-linked immunosorbent assay of antisera from rabbits immunized with dichloroacetic anhydride-modified keyhole limpe hemocyanin. Test antigen was dichloroacetic anhydride-modified rabbit serum albumin.

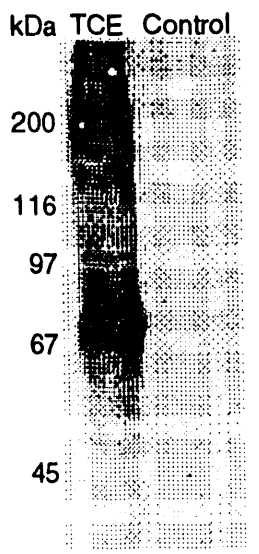


Figure 5. Immunoblot of mouse hepatic cytosolic protein separated by polyacrylamde gel electrophoresis. Proteins were blotted and stained with anti-TCE antibodies. TCE, mice treated with TCE (1000 mg/kg ip in corn oil); Control, vehicle control.

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

Milestones Achieved

1. Synthesis of TCE oxide. TCE oxide is another putative reactive metabolite of TCE. This reactive metabolite differs from dichloroacetyl chloride in two ways: 1) this reactive species may react with different amino acid residues on proteins, giving rise to different adducts; and 2) the adducts formed will have three chlorine atoms. Thus, the antisera produced against dichloroacetyl chloride-derived adducts may not recognize adducts from this metabolite. The known variation in human metabolism suggests that we may need different types of antibodies in order to detect all exposures. Thus, immunogens will be prepared from this metabolite and used to raise different antsera.

   TCE oxide was synthesized by oxidation of TCE in the presence of *tert*-butyl hydroperoxide at 60°C for 30 hr. The product was distilled over a spinning-band column; the dichlrooacety chloride contamination was removed by washing the product with 1N NaOH, and drying over sodium sulfate. The product was stable for several months at -80°C.

Summary - Year 2

During the first year of this project, we developed methodology that will allow us to detect and identify TCE-protein adducts *in vivo*. We have in place analytical methodology, including HPLC and mass spectrometry, that will be utilized for structural elucidation of protein adducts. In addition, we have raised polyclonal antibodies against TCE adducts, which will assist us in adduct identification, as well as provide us with the basis for an immunoassay to detect exposure in experimental animals and humans.

Milestones and Deliverables Planned for Year 3

1. Optimize high performance liquid chromatographic (HPLC) separation of serum albumin tryptic peptides.

2. Map unmodified human serum albumin using tandem mass spectrometric analysis of purified peptides.

3. Perform chemical modification of human hemoglobin and serum albumin *in vitro* with the reactive metabolites (dichloroacetic anhydride, TCE oxide, chloraldehyde); optimize procedure as necessary.

4. Analyze modified hemoglobin and serum albumin using electrospray ionization and/or time-of-flight mass spectrometry.

5. Purify tryptic peptides from modified human hemoglobin and serum albumin by HPLC and/or immunoaffinity chromatography as described above.

6. Analyze tryptic peptides from modified human hemoglobin and serum albumin by tandem mass spectrometry; determine specific sites of adduction by comparison with hemoglobin and serum albumin maps.

7. Prepare immunogen by chemical modification of keyhole limpet hemocyanin or human hemoglobin tryptic peptide fragments; immunize rabbits, collect and characterize antisera.

8. Identify additional chemicals of interest for biomarker development.
   a. perform literature review of candidate chemical
   b. initiate protocol development

Deliverables:

- Optimization of serum albumin tryptic peptide HPLC purification system (09/94)
- Mass spectral analysis of unmodified serum albumin (09/94)
- Map of unmodified human serum albumin (10/94)
- Mass spectral analysis of tryptic peptides from modified human hemoglobin and serum albumin (12/94)
- Preparation of immunogen; immunization of rabbits (02/95)
- Identification of putative hemoglobin/serum albumin adduct(s) (05/95)
- Characterization of antisera (06/95)
- Identification of chemical of interest for biomarker development (06/95)
- Initiate biomarker development for additional chemical of interest (07/95)
- Manuscripts and abstracts

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

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

Description:

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.

Background:

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 groundwater 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.

Milestones and Deliverables Achieved - Year 2:

1. Optimize isolation of rat and mouse hepatocytes
   Proposal of animal use submitted for review by Animal Review. Committee approved 10/22/93 Isolation and culture of rat and mouse hepatocytes have been achieved; protocols for these procedures have been developed

- Proposal and approval of animal use (34)
- Perfusion Procedures - Mouse and Rat (35)

2. Obtain human liver cell lines for culture
   Cells of the HepG2 human liver cell line have been obtained and are being maintained
   Cells of the Hep3B human liver cell line have been obtained and are being maintained

3. Optimize assays for determining peroxisome proliferation
   a. palmitoyl CoA oxidase activity
   b. carnitine acetyltransferase activity

   - Assay protocols for measuring palmitoyl CoA oxidase and carnitine acetyltransferase have been developed (36)

4. Optimize assay for determining DNA synthesis

   - An assay protocol for measuring DNA synthesis (^{3}H-thymidine uptake) in rat and mouse hepatocyte cultures and in HepG2/Hep3B cells has been developed (37)

5. Optimize hepatocyte culture conditions for studies on TCE-induced peroxisome proliferation and induction of DNA synthesis
   a. dose-response relationship
   b. time-response relationship

   No appropriate means of delivering TCE to the cell cultures could be found due to (a) the extreme insolubility of TCE in aqueous solutions, such as the cell culture medium and (b) the necessity of using a shared-use incubator for maintaining the cell cultures. Attention has been shifted to the proposed reactive metabolites of TCE: TCA and DCA.

   Experimental protocols for determining TCA-induced peroxisome proliferation and induction of DNA synthesis in rat and mouse hepatocyte cultures have been developed

   Preliminary data on TCA-induced peroxisome proliferation in mouse hepatocytes have been obtained

   Rat hepatocytes have been treated with TCA; samples have been collected and stored for enzymatic analysis

   Preliminary data on the dose-response relationship for induction of DNA synthesis in rat and mouse hepatocytes have been obtained

6. Optimize HepG2/Hep3B cell culture conditions for studies on TCE-induced peroxisome proliferation and induction of DNA synthesis
   a. dose-response relationship
   b. time-response relationship

   Experimental protocols for determining TCA-induced peroxisome proliferation and induction of DNA synthesis in Hep3B and HepG2 cell cultures have been developed

   HepG2 cells and Hep3B cells have been treated with TCA; samples have been collected and stored for enzymatic analysis

   Preliminary data on the dose-response relationship for induction of DNA synthesis in HepG2 and/or Hep3B cells have been obtained

7. Compare induction of peroxisome proliferation by TCA with that of a known peroxisome proliferator (*eg.* clofibrate)

   Comparative studies with clofibrate have begun; no preliminary data as yet

8. Compare the induction of DNA synthesis by TCE (TCA) with that of a known mitogenic agent (*eg.* epidermal growth factor)

   Preliminary comparative data for epidermal growth factor in rat and mouse hepatocytes and in HepG2 and/or Hep3B cells have been obtained

9. Initiate a collaboration with MUSC's liver transplant unit to obtain human liver samples for establishing human primary hepatocyte cultures

   Dr. Adrien Rubin and Dr. Robert Galbraith (both from the MUSC Liver Transplant Unit) have been approached about the possibility of obtaining human liver samples for isolation of hepatocytes.

Milestones and Deliverables Planned for Year 3

Milestones:

1. Initiate studies on TCE-metabolite induced peroxisome proliferation and enhancement of DNA synthesis in rat and and mouse hepatocyte cultures and in the HepG2 and Hep 3B human hepatoma cell lines

2. Optimize hepatocyte culture conditions for studies on TCE metabolite-induced peroxisome proliferation and induction of DNA synthesis
   a. dose-response relationship
   b. time-response relationship

   - Data on the dose-response and time-response relationship for DCA-induced peroxisome proliferation in rat and mouse hepatocytes and human hepatoma cell lines. (12/94)

- Data on the dose-response and time-response relationship for DCA induction of DNA synthesis in rat and mouse hepatocytes and human hepatoma cell lines. (12/94)

- Data on the dose-response and time-response relationship for TCA-induced peroxisome proliferation in rat and mouse hepatocytes and human hepatoma cell lines. (6/95)

- Data on the dose-response and time-response relationship for TCA induction of DNA synthesis in rat and mouse hepatocytes and human hepatoma cell lines. (6/95)

3. Compare the ability of TCE metabolites to induce peroxisome proliferation with that of a known peroxisome proliferator (*eg.* clofibrate)

   - Comparative data for clofibrate and epidermal growth factor in rat and mouse hepatocytes and human hepatoma cell lines. (6/95)

4. Compare the induction of DNA synthesis for TCE metabolites with that of a known mitogen (*eg.* epidermal growth factor)

5. Obtain outside contact for learning human hepatocyte isolation. This will provide expertise for future studies to examine this phenomenon in human hepatocytes.

5.1.5 Protein and Peptide Mass Spectrometry in Relation to EHAP Research

Project Director :	Daniel R. Knapp, Ph.D.
Co-Investigator:	David McMillan, Ph.D.
Co-Investigator:	Mark Busman, Ph.D.

Description:

This project entails development of methodology and structural characterization of proteins and peptides in relation to EHAP research projects initially including:

1. Studies of Metal Induced Autoimmune Diseases (Analysis of HLA-presented antigenic peptides.)
2. Studies of Biomarkers of Toxic Chemical Exposure (Analysis of hemoglobin and albumin adducts of reactive metabolites of toxic chemicals.)

The methodology to be developed for and applied in these projects involves online microbore HPLC-mass spectrometry (MS) and tandem mass spectrometry (MS/MS). In the case of the autoimmune disease studies, the methods were to be used to characterize complex mixtures of HLA bound antigenic peptides. In the case of the biomarker studies, the methods will be used to characterize peptides in mixtures from cleavage of adducted proteins. The milestones and deliverables projected for the year were as follows:

Progress During the Year on the Project Milestones:

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 quantitites originally envisioned. However, we still should be able to provide the needed analyses for samples enriched in specific peptides is 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 continuing on interface enhancements to enable computer control of quadrupole resolution and offset as well as all of the ion optical element potentials.

3. Assembly of microbore/capillary HPLC system.

   Micobore HPLC equipment was purchased from the low bidder, MicroTech Scientific, and received. Performance tests in this laboratory led to questions as to whether the equipment met the bid specifications. A decision was made to return the equipment and purchase from the next bidder (Applied Biosystems) equipment with an established performance record. A dispute ensued with MicroTech Scientific who claimed they could meet specifications if given more time. Given the time constraints on the equipment funding, a compromise was negotiated whereby one of the two MicroTech pumps would be returned and an ABI pump purchased. Work is underway on optimizing performance of the MicroTech pump while awaiting delivery of the ABI pump.

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

   Awaiting receipt of ABI HPLC pump.

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. Construction of the trap is underway in the Department of Pharmacology machine shop.

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

   Awaiting completion of the liquid nitrogen cold trap.

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 and albumin adducted with TCE metabolites.

    Work has been initiated on fractions collected by offline HPLC (see D. McMillan progress report).

Other Relevant Progress:

We have secured funding from another source to implement electrospray mass spectrometry on the JEOL HX110/HX110 high mass high performance tandem mass spectrometer. The ESI source for this instrument has been ordered and is expected to be delivered in Fall, 1994. ESI capability on this instrument will be very useful for the proposed work.

Summary:

Little progress was made on this project due to multiple complications in purchasing the needed equipment. All equipment will be delivered by June 30, 1994, and thus be available for initiation of this project in year 3 of the program.

Publications:

No publications have resulted from this project.

Milestones Planned for Year 3:

1. Interfacing of microbore/capillary HPLC to the electrospray ion source on the Nermag R30-10.
   - Assembly of microbore/capillary HPLC sytem (8/94).

2. Implementation of flow-FAB ion source on the JEOL HX110/HX110 four sector tandem mass spectrometer.

3. Interfacing of microbore/capillary HPLC to the flow FAB ion source on the JEOL HX110/HX110.

4. Installation of electrospray ion source on the JEOL HX110/HX110.

    - Interfacing of microbore/capillary HPLC to the electrospray ion source on the Nermag R30-10 (9/94).

5. Implementation of online HPLC aelectropsray ionization MS on the JEOL HX110/HX110.

    - Implementation of flow-FAB ion source on the JEOL HX110/HX110 four sector tandem mass spectrometer (8/93).

6. Synthesis of model antigenic peptides for analytical methods development.

    - Interfacing of microbore/capillary HPLC to the flow FAB ion source on the JEOL HX110/HX110 (9/94).

7. Implementation of online HPLC-MS and MS-MS analysis of peptide in mixtures.

    - Synthesis of model antigenic peptides for analytical methods development (10/94).

8. Establishment of sensitivity limits for online HPLC-MS and MS-MS analysis of peptides.

    - Implementation of online HPLC-MS and MS-MS analysis of peptide in mixtures (11/94)
    - Establishment of sensitivity limits for online HPLC-MS and MS-MS analysis of peptides (12/94).

9. Analysis of HLA presented antigenic peptides from Beryllium autoimmune disease studies.

    - Analysis of HLA presented antigenic peptides from Beryllium autoimmune disease studies (10/94).

10. Analysis of tryptic digest peptide mixtures from hemoblobin adducted with TCE metabolites.

11. Ongoing analyses of peptide mixtures from hemoglobin adduct digests and HLA peptide extracts. (11/94 - 6/95).

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

HEALTH EFFECTS

SPECIFIC AIM: To evaluate estimated cancer risks from low-dose and low-dose rate exposures which are traditionally modeled from acute high-dose exposures. Also we will evaluate the biological effectiveness of high LET radiation exposures (namely neutron).

HYPOTHESIS: For a given exposure, cancer risks are decreased for low dose-rate exposures of low LET (gamma) and increased for high LET (neutron). Further, for a given dose, neutron induced cancer incidence greatly exceeds that for gamma.

METHODS: Data from the Argonne National Laboratory's Janus program will be used. This program previously conducted extensive experiments involving mice exposed to various doses and dose-regimens and held for their lifetime with pathology analysis carried out at time of death. Exposures involved either gamma or neutron and where either acute, 24 times weekly or 60 times weekly. Log-linear Poisson regression models of increased relative risk are used with linear or linear-quadratic dose effects. This is the same class of models which the NAS/NRC's BEIR V Committee used for the analysis of human cancer data for developing their radiation-cancer risk estimates. Dose rate effectiveness factors (DREF) will be calculated for major modeled cancer types. Also confidence intervals will be determined. Similar factors for RBE's of neutrons will be determined. What is of particular importance is whether or not these factors vary with dose and time?

RESULTS: Connective tissue tumors and several subgroups have been modeled as well as epithelial tumors. The models well described the data for the data rich connective tissue tumors. It turned out that a DREF of about 2 is a very good value for these tumors and did not vary by sex or time. RBE's are more complex and work continues. The DREF fits for neutrons are yet to be modeled.

SIGNIFICANCE: The issue of low dose-rate radiation cancer risks remains critical and unresolved (see BEIR V) for radiation standard setting. A systematic analyses of existing animal data is the best way to understand this issue and possibly resolve the risk question.

HUMAN EXPOSURE

SPECIFIC AIM: To develop improved methods of evaluating human exposures to ionizing radiation.

HYPOTHESIS: Methods of physiologically-based pharmacokinetic modeling and simulation are essential to dose-response evaluations of human health effects. Precision of these estimates are the key to the evaluation of health effects.

METHODS: 1) Incorporate the analytical tools of systems science and engineering to the theoretical and methodological research of physiologically-based pharmacokinetic models.
2) Monte Carlo techniques are used to evaluate the precision of human exposure estimates developed using fate-transport models. A sensitivity model will be developed for a search based optimization method for the Monte Carlo sampling. This will help determine the maximum sensitivity of parameters in the models.

RESULTS: Techniques for fast solutions to physiologically-based pharmacokinetic models have been published. The research plan for a working sensitivity model for one type of exposure analysis models is underway.

SIGNIFICANCE: It is critical to quantitatively evaluate the amount of uncertainty in output values of environmental exposure models of low-dose radioactive materials.

MAJOR MILESTONES & DELIVERABLES

Year 2

	Major Milestones	Product
Product 1:	Algorithm for computing solutions to PBPK modeling and simulations	Paper presented at SPECTRUM '94 (Nuclear Hazardous Waste Management International Topical Meeting Aug. 14-18, 1994, Atlanta.) Three presentations at Soc. Risk Analysis, Dec. 1993. (38)
Product 2:	Preliminary models of connective tissue tumors for gamma and neutron exposures	Computer data files and model outputs (Information is on file in Dr. Hoel's office at MUSC.)

Year 3

Product 3:	Completed analysis of connective tissue tumors with dose-rate effectiveness factors and relativeness biological effects for neutrons determined	Completed manuscript

Product 4:	A working sensitivity model for one type of exposure analysis/risk analysis model	Meeting abstract (paper in Year 4)
Product 5:	Development of a search based optimal sampling algorithm for Monte Carlo analysis of fate-transport models.	A working computer program.

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.

Goals, 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 Achieved in Year 2

1. The comprehensive survey of the literature, begun in Year 01, has identified a bibliography of approximately 300 publications. The articles are being reviewed and analyzed by a graduate student. It is planned to assess the quality of the articles and to publish the resulting bibliography for distribution.

   - Due to its volume, the bibliography is not included in this report. It is on file in the survey center.

2. Pilot population survey - a pilot project involving interviews of nearly 1,000 households of residents in Georgia and South Carolina was completed. The randomly selected sample tested the variation in risk perceptions proximal to the Savannah River Site. Preliminary results were presented at the 1993 annual meeting of the Society for Risk Analysis, as follows:
   - Abstracts and posters: Perceived Risks in Geographic Areas Proximal to a Nuclear Production Facility; (39)
   - Abstracts and posters: The Influence of Printed Media on Perceived Risk (40)

   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 on several occasions:

   NIH sponsored meeting on environmental justice;
   EHAP seminar on epidemiology;
   Stone Container Corporation (Savannah);
   Union Camp Corporation (Savannah).

   - One technical report to be the basis of two future manuscripts (41)

3. Politician survey - Results from the pilot population survey prompted the design of a politician assessment. A significant proportion of the population in Georgia and South Carolina indicated contact with political leaders regarding environmental concerns. Legislators in Georgia and South Carolina were contacted by mail regarding the quantity of letters, phone calls, and personal communications regarding environmental controls and in particular the Savannah River Site. The Survey was implemented in June and will be analyzed during the 1994 summer.

4. An expert advisory committee was organized with representatives from MUSC, Agency for Toxic Substance and Disease Registry, Centers for Disease Control and Prevention, American Cancer Society, Society for Risk Analysis, University of Cincinnati, Department of Energy, and the German Radiation Health Institute. The first meeting of the committee was held February 24 and 25. Members of the committee are:

   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.

The two-day meeting and reception were 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. It will meet twice a year in continuing to assess the program.

The notes and recommendations of the expert advisory committee were assembled and edited into a report. These recommendations will be used to modify the analytic efforts and to assist in the development of Year 03 and 04 plans.

- Report from expert advisory committee - see deliverable (21)

5. Participated in meetings:
DOE-EM Programmatic Environmental Impact Statement Risk Assessment Model Review Workshop,

American Industrial Health Council - "Realistic Estimates of Risk: American at a Critical Junction,"

State Health Agreement meeting in Gaithersburg, Maryland on December 1-2, 1993, sponsored by the Environmental Health and Safety Division of DOE. The eight state program participants (including SRRHIS), addressed by Dr. Tara O'Toole, seek to pool their efforts in public information surveillance, dissemination, and impact evaluation.

6. Meetings with:
Dr. Todd Stong (Coleman Research) to develop a detailed risk assessment program agenda.

Dr. Richard Sebastian to discuss assessment of airline pilots and the health effects of low level (cosmic) radiation.

7 Designed and began Hilton Head/Beaufort Tritium education project. In the period, January - March, 1994, a three person subcommittee of the program Advisory Committee, was named to develop and oversee the Lackland project to promote public awareness about health effects associated with current and anticipated future tritium releases from the SRS enterprise:

Dr. Roy Eckart, Chairman of the Department of Mechanical and Nuclear Engineering, University of Cincinnati;

Dr. David McCallum, Risk Communicator, Washington, DC;
- Dr. Lawrence Needham, Toxicologist, Centers for Disease Control and Prevention.

The project is actively seeking data on the concentration of tritium in the Savannah River water. After that another conference call will review dose/health risk and the risk communication process.

8. Dr. Dunbar is serving as a **member of the Steering Committee for the American Statistical Association**, "1994 Conference on Radiation and Health," and will chair the session on "Radiation Dosimetry."

9. Presentations:
American Association of Central Cancer Registries - This presentation dealt with standard methodology in case ascertainment, data exchange, and data quality assessment. These studies confirm the need for high quality in cancer registration for risk and health assessment. In addition, collaborative arrangements were instituted between registries associated with DOE sites throughout the country.

"Symposium on Health Research and Needs to Ensure Environmental Justice," February 1994, Arlington, Virginia, sponsored by NIEHS.
- Poster (42)

11 Geo-Coding Project - A collaborative program to establish a comprehensive geo-coding geographic area. The collaboration is with the State Budget and Control Board, the custodian of the data and associated network. Arrangements are being made to use two summer research students to be trained to implement the quality control methodologies. Cancer registry data will be included in the study.

Projected Milestones and Deliverables Planned for Year 3

1. Assessment of Georgia and S. C. legislators with regards to environmental health.
   - Technical report.

2 Analysis of risk perception variation by race
   - Technical report

3. Quantification of recommendations and advice from expert advisory committee.
   - Technical report

4. Risk perception as related to diet and environmental concerns.
   - Technical report/manuscript

5. Completion of pilot geo coding of selected geographic areas

- Technical report.

6. Documentation of geo-coding methodology

   - Abstract and scientific presentation

7. Assessment of cancer cases in small geographic areas

   - Technical report

8. Expansion of geo-coded areas.

   - Report

9. Analyses of multiple variables in small geographic areas.

   - Manuscript

5.3 Information Support and Access Systems	
Director:	Tom Basler, Ph.D.
Systems Analysis:	Richard Gadsden, CCIT
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 has continued through Year 2. The major focus during the second year of the grant has been 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've begun to examine advanced techniques to assist the user in identifying and retrieving as much relevant data as is possible from a wide range of sources. We've identified information needs and made a number of environmental and health related databases available to our researchers. These databases provide the basis for developments of our One Door Access System (ODAS). During the year we have experimented with and developed two emerging information sharing technologies, namely gopher and World Wide Web (WWW) mosaic servers. We've completed the implementation of the MUSC gopher server and have an initial prototype version of our WWW server on-line. We've also completed extensive surveys of users to establish needs, surveys of information sources, and developed a first-cut prototype to prove the information access system design concepts. We've also completed implementation of our EHAP network and have supported our outreach and public involvement "Crossroads of Humanity Series" through development of an expert database.

During year 3, our ODAS prototytpe will be extensively demonstrated. Interaction with researchers and others in the health and environmental communities will provide the basis for our continuing information access system developments. We'll also be completing installation of our SGI workstations and completing our MUSC network and research computing installations. We'll continue improving our gopher server and be making our mosaic server available.

Milestones Achieved, Year 2

1. We completed the evaluation and selection of a systems development contractor, Coleman Research Corporation.

2. We completed the design and implementation of a database to support the Crossroads of Humanity Series. This database is used to identify and provide information on the over 3000 people who have or will be involved in the public outreach programs. This database also enables us to easily identify and contact experts who deal with a variety of environmental issues. Its implementation is an important accomplishment leading to fulfillment of one of the major grant objectives - "Develop a pool of talented scientists and experts in cleanup activities, especially in human health aspects".

3. The design and implementation of the internal EHAP network has been completed. All computers in EHAP are connected to the university network, this has made possible developments in gopher and mosaic technologies. We completed the installation of servers to provide NIS services, NFS servers, implemented new Internet services, and the SGI workstations. All of this was necessary to support our gopher, mosaic, and information access system developments.

4. Completed the survey, selection, and installation of environmental and health related databases. These databases provide the information necessary to our research efforts as well as the basis for developments of our information access

system. The CDPLUS Ovid search software has been installed on a DEC Alpha server, with the MEDLINE, Cinahl, Health, Current Contents, PsycInfo, and CancerLit databases.

5. The Needs Assessment Report was completed and published on June 30 as planned. The first step in identifying the "environmental" information needs was to survey leading individuals in related fields who represent the information customers we expect to serve. The following lists the fields represented by our interviewees.

   - Research & Academics - toxicologists, pharmacologists, microbiologists, epidemiologists, librarians, systems developers & others
   - Health Practitioners - pathologists, family medicine practitioners, pharmacists, and nurses
   - Risk Assessment professionals

   The survey ask for input on specific information needs, current sources, and prioritized those needs. The results give us the basis for making decisions on what types of data to include in our "one-door" access system.

   - Needs Assessment Report (43)

6. The Database Survey Report was completed and published on June 30 as planned. This report reviews available environment/health databases, evaluates their relevance to the needs of MUSC/EHAP, and provides technical and cost information on each. In all, 127 environmental/health related databases were identified in the research effort. The database producers and vendors are grouped into three categories: government, nonprofit, and commercial. This report coupled with the needs assessment report will provide the basis for establishing the next phase in our information access system development.

   - Database Survey Report (44)

7. The first One Door Access System (ODAS) prototype development was completed in June. This first prototype access six locally mounted databases. It responds to queries by searching all of the data sources available for information on the requested topic. It demonstrates how queries can be specified, how different data sources can be chosen by the user, and how information from multiple sources can be returned. We'll demonstrate this first prototype to researchers and physicians across the university and solicit feedback for improvements and enhancements for the next version of the prototype.

8. Experimental agreements have been signed with the NLM and the UMLS data has been delivered to EHAP on CD-ROM. UMLS contains over 450 megabytes of data. It provides information about biomedical concepts, their representation in different vocabularies and their thesaurus, and their co-occurrences in selected databases. By integrating the UMLS data with the ODAS, the ODAS will be able to provide users with a method of narrowing search criteria and relating concepts

prior to initiating searches. This addition will provide the ODAS with a broader capability to recognize similarities between data categories and to relate concepts.

9. The EHAP World Wide Web (WWW) Server project has just gotten underway. It will provide a multi-media presentation that will describe EHAP and its related projects using video, graphics, sound and text. This server will be accessible by anyone with an Internet connection using NCSA's Mosaic WWW browser software, which is available for Macintosh, Microsoft Windows and X Windows (UNIX) platforms. Development of this server and it's contents will initially be performed by the EHAP Systems Administrator, a Coleman Research Systems Engineer and an EHAP Public Information Specialist. A prototype will be developed and presented to various MUSC and EHAP personnel and feedback will be used in further development. Presently, there are two test WWW servers (Macintosh and UNIX) and the default "Home Page" prototype is being developed. Video, graphics, sounds and text from various EHAP events are being digitized for the prototype. Like our gopher server, this technology is being investigated in an effort to identify and develop platforms and systems capable of making environmental hazard information available to the widest possible audience.

10. Registration of the EHAP Gopher server with the University of Minnesota and its full production implementation began on April 1. Research for useful EHAP related gopher sites is periodically being performed by the EHAP librarian, the EHAP Systems Administrator, and an EHAP Public Information Specialist. As useful sites are found, links to these sites are made available through the EHAP directory location on the MUSC Gopher Server. The EHAP directory on the MUSC Gopher Server contains information about the EHAP program and various related projects, as well as links to other gophers around the world containing useful information related to health, science and the environment.

11. Classes on information use and management have been held for EHAP students and faculty. Use of communications tools has also been taught in seminars and individually. Troubleshooting support is available. Reference support in EHAP topics is now established and ongoing. Collection identification and acquisitions is ongoing and connected to both educators and researchers in the EHAP project and peripheral areas.

Milestones Planned, Year 3

1. We'll complete installation and networking of all SGI and DEC alpha workstations and initiate a program of advanced computational and modeling support for researchers.

2. We'll continue development of our gopher server through identification and connection of environmental resources across Internet.

3. Our first implementation of a WWW server will be started no later than mid-year. This will provide the basis for developing futher data sharing techniques for interested communities, industries, and other research organizations.

4. We'll design and implement a new "expert" database in support of our outreach and community involvement programs in the Crossroads of Humanity Series program.

5. The ODAS prototype system will continue to be refined and improved. We'll concentrate efforts on:
   integration of the NLM's UMLS,
   interactive update of the ODAS Knowledge base, which will facilitate the addition of new databases to the system,
   capability to "launch" search results into an external application,
   an information reference tool that provides the database names, descriptions, and point-of-contact information associated with specific categories of data.

6. Efforts will intensify in the education of faculty, students and researchers in the use of environmental information. Particular efforts in the support of the Environmental, Occupational and Agricultural program will be upgraded. Demonstrations of the database systems to other groups (statewide) will begin (September, 1994) Database sharing with local universities will be put into effect.

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 Program (SCSFPRP), and 2) develop a consultative/support network in environmental medicine for the faculty and residents of the SCSFPRP. The success of this project is dependent upon the development of an Environmental Medicine Curriculum Committee (EMCC) composed of at least one faculty member from the seven SCSFPRP sites. The success of the committee is dependent on a team approach among the members and on the EMCC having access to an academically-based resource to develop curriculum for their sites and to be on call to their residents and faculty for environmental medicine consultations. The success of the curriculum depends on its relevance as an integral part of the core discipline of family practice, recognized by residents and faculty role models.

Milestones and Deliverables (bullets) for the Period:

Curriculum

1. An EMCC committee consisting of faculty appointed by the seven chairs of the SCSFPRS was formed. Meetings were held with individual EMCC members at their sites in order to learn their needs/concerns for environmental and occupational

medicine curriculum, to discuss EMCC goals and to encourage active participation in the committee (7/93).

- Roster of SCSFPRP/EMCC members including two additional faculty who volunteered for the committee and dates of the site meetings (45)

2. The EMCC held its first meeting/workshop September 2-3, 1993 in Columbia, SC. The committee agreed on goals and developed consensus statements. Additionally the committee agreed to participate in three EOM research projects to be completed by the next workshop. The committee requested the following four curriculum outlines be developed for discussion at the next meeting: (a) the longitudinal implementation of EOM over the three year residency curriculum, (b) an eight hour self-study package, and (c) one week and (d) one month electives. A summary of the meeting will appeared in the October 1993 issue of the *Environmental Medicine Update.*

3. The EMCC held its second meeting/workshop December 2-3, 1993 in Columbia, SC. A summary of the meeting will appeared in the January 1994 issue of the *Environmental Medicine Update.*

   The meeting agenda included reports on the three EOM research projects which were initiated and completed since the last EMCC meeting in September. These projects involved all seven family medicine residencies and included: 1. documentation of existing EOM curriculum at each site, 2. a review of a random sample of patient records for sentinel EOM events, and 3. a survey of family medicine residents for their perceptions of and need for EOM curriculum.

   - Report - Environmental & Occupational Medicine Curriculum Survey / Statewide Family Practice Residency Program (46)

   - Report - Environmental & Occupational Medicine Patient Chart Review / Statewide Family Practice Residency Program (47)

   - Report - Environmental & Occupational Medicine Survey of Family Medicine Residents / Statewide Family Practice Residency Program (48)

   The committee also approved a curriculum matrix for the implementation of EOM within the residencies. This includes longitudinal curriculum over the three year residency and three elective formats (eight hours, one week and one month).

   - Environmental and Occupational Medicine Curriculum Matrix / Statewide Family Practice Residency Program (49)

   The EMCC discussed methods for and content of curriculum modules to be developed for the longitudinal and elective curriculum. The committee authorized the project staff to begin work on the following longitudinal curriculum modules: 1. EOM History Taking, 2. Clinician Response to EOM Hazards, 3. Risk

Assessment and Risk Communication, 4. EOM Data Bases and Consultants and 5. EOM in Private Practice.

4. The EMCC held its third workshop March 15-16, 1994 in North Myrtle Beach, SC. The meeting summary is reported in the *Environmental Medicine Update* (Volume 1, No. 9).

   The meeting agenda included review and comment on the following five environmental and occupational medicine (EOM) longitudinal curriculum modules: 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. Module 6, EOM Site Visit, was not ready for review. Each module consists of a slide lecture with script and an interactive computer program. The committee voted to merge two of the modules (modules 2 and 3 above).

5. On June 30, 1993, the following environmental and occupational medicine core curriculum modules were delivered to the Environmental Medicine Curriculum Committee. Each module consists of teaching slides, script, interactive pc program, evaluation forms and references.

   - Module 1-Environmental and Occupational Medicine History for Family Physicians (50)
   - Module 2-Communicating Environmental and Occupational Risks to Patients: A Guide for the Family Physician (51)
   - Module 3-Environmental and Occupational Medicine Resources for the Family Physician (52)
   - Module 4-Environmental and Occupational Medicine in Private Practice: Choices for the Family Physician (53)
   - Module 5-Using Hospital Site Visits for Teaching Environmental and Occupational Medicine (54)

The modules were submitted to EHAP along with the fourth quarter on July 1, 1994.

6. The monthly newsletter, *Environmental Medicine Update*, was published August 1, 1993 through June 30, 1994. The objectives of the newsletter are to report on the activities of the EMCC and to stimulate committee members concerning recent developments in environmental medicine.

   - *Environmental Medicine Update* - Volume 1, Numbers 1-11. (55)

7. Forty-three EOM lectures were presented during the period.

   - Lectures described in the July 1993- June 1994 Summary Reports (56)

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 224 environmental/occupational medicine cases during the period.

   - Cases described in the July 1993 -June 1994 Summary Reports (see 56)

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 Program. Informational and rotary file cards describing the consultative and case research services of the Environmental and Occupational Medicine Office were distributed to the Environmental Medicine Curriculum Committee on June 29, 1993. These will be distributed to the faculty, residents and staff of the Statewide Family Practice Residency Program.

   - OEMO information card and OEMO rotary file card (57)

Milestones Planned for Year 3:

Professional Support Network

1. Provide EOM consultations to the Statewide Family Practice Residency Program.
2. Provide EOM case research to the Statewide Family Practice Residency Program.
3. Publish on a monthly basis the newsletter, Environmental Medicine. Update, to advise members of the Environmental Medicine Curriculum Committee and of committee activities and current issues in EOM.

Curriculum

1. Develop Macintosh versions of the interactive pc programs developed for the EOM core curriculum delivered last fiscal year (est. 9/1/94).
2. Develop eight elective EOM curriculum modules (est. 6/1/95).
3. Update EOM core curriculum modules (est. 6/30/95).
4. Determine if core and elective EOM curriculum can be adapted by nursing, dental medicine & pharmacy (est. 3/1/95).
5. Survey alumni of the Statewide Family Practice Residency Program to determine interest in EOM continuing medical education (est. 12/1/94).

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) I proposed to develop 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** were: 1) develop an assessment tool and a survey pool 2) implement the tool; 3) analyze the results; and 4) report the conclusions both as a report to EHAP and as a paper. These specific objectives were to be accomplished at a rate of one per quarter.

B) I proposed to take an existing undergraduate course and develop it 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 was previously focused exclusively on the nomenclature of organic chemistry. The **specific objectives** were: 1) to develop the course material; 2) test on the presented material; and 3) assess the students' opinions concerning the inclusion of environmental health materials in the course curriculum.

The rational for these proposed studies 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 - Environmental Hazards Assessment Program

1. A survey instrument was developed and a trial survey was taken and analyzed (9-93).

2. The survey instrument was refined, the survey field was defined and the survey was distributed (12-93).

3. The survey results were collected (477 surveys returned for a 53% return rate), cataloged, entered into a database, an analysis profile written, and the data was analyzed mathematically (3-94).

4. The data has been analyzed conceptually, presented at the American Association of Colleges of Pharmacy (07-94) as a poster and written for submission to Pharmaceutical Education (8-94).

   - Poster and abstract (58)

5. The results of the survey will be mailed to the 287 responders who requested this information.

Milestones - BS Level Medicinal Chemistry/ Environmental Health Course Development.

1. The course material was developed and taught concurrently (12-94).

2. The students were tested on the material and the students' perception of the utility of the material was surveyed as part of the course evaluation (relevant items abstracted from the survey are attached) (3-94).

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

Project 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 which 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 Achieved in Year 2

1. Eleven students enrolled in the doctoral program in risk assessment
   They are: Richard Daehler-Wilking, Michael Pisarcik, Jennifer Schultz, Paul Nietert, Tom Radivoyevitch, Kevin Nelson, Len Balthis, Joyce Nicholas, Bradley Venner.

   - Profile sheets (59)

2. Proposal for Master of Science degree in environmental studies prepared, approved by the Commission for Higher Education of the State of South Carolina for consideration for the offering of a new degree program. Application for Admission for the Master of Science in Environmental Studies Program designed.
   To date 280 applications mailed to prospective students.
   To date 12 students accepted for the Fall Semester 1994.

   - Award letter (60)
   - Application form (61)

3. Student Handbook for the Master of Science in Environmental Studies Program designed.

   - Copy of Handbook (62)

4. Steering Committee formed to undertake the details of running the new Master of Science program in Environmental Studies. This Committee also serves as the Admissions Committee for the Program.

   Committee Members:
   University of Charleston
   Dr. Lou Burnett, Chairman, Dept. of Biology
   Dr. Michael Katuna, Chairman, Dept. of Geology
   Dr. Andy Felts, Director of the Institute for Public Affairs and Policy Studies

   Medical University of South Carolina
   Dr. Rebecca Knapp, Professor, Dept. of Biometry and Epidemiology
   Dr. JoEllyn McMillan, Assistant Professor, Dept.of Pharmacology
   Dr. Michael Schmidt, Assistant Professor, Dept. of Microbiology and Immunology

5. Spring Seminar Series for Environmental Risk Assessment students developed under the direction of Dr. David Jollow, Department of Pharmacology and Dr. Zhen Zhang, Department of Biometry and Epidemiology. Seminars are scheduled for every Wednesday throughout the Spring Semester with various MUSC faculty as speakers.

   - List of faculty participating (63)

6. Brochure designed for the Master in Environmental Studies Program. Five thousand brochures were mailed to various departments in institutions throughout the United States for the purpose of recruitment.

   - Brochure (64)

7. Poster for the Ph.D. track in Environmental Risk Assessment designed and mailed to colleges and universities throughout the Southeast.

   - Poster (65)

8. Courses in Environmental Biology and Environmental Health Risk Assessment developed and offered to students for Fall 1993 and Spring 1994 respectively.

   a. 11 students successfully completed course in Environmental Biology
   b. 13 students successfully completed course in Environmental Health Risk Assessment

   - Syllabi for courses (66)

9. Assistant Professor in Health Policy selectedDr. David R. Graber, appointed 8/1/93

   - Curriculum vitae (67)

10. Recruitment of environmental microbiologist and risk analyst faculty. Three candidates interviewed for the position. Dr. Pamela Morris and Dr. Harold May were selected.

    - Advertisement for position placed in SCIENCE (68)
      Copies of Seminar notices
      C.v.'s and letters of appointment

11. Course offerings for the Master of Science in Environmental Studies Program developed and internal approval obtained.

    - Complete list of Program course offerings (69)

12. Summer undergraduate research program in environmental studies initiated with enrollment of seventeen students

    - Reports (70)

13.. Formation of an external advisory council to provide annual guidance on the environmental graduate programs.

Milestones Planned for Year 3

1. Fifteen students enrolled in the doctoral program in risk assessment.

2. First class enrolled in the Master of Science Program in Environmental Studies.

3. Courses in environmental studies offered to all graduate students and continue to develop course curriculum for courses offered by the University of Charleston.

4. Development of an environmental (occupational) health nurse practitioner track in Master's degree Primary Care Nurse Practitioner Program. Also continuing educational (CE) workshops targeted to nurses and undergraduate and graduate faculty.

5. Poster for the Master of Science in Environmental Studies Program designed and mass mailout planned for recruitment for the Spring1995 Semester.

6 Summer Undergraduate Research Program in environmental studies in progress with enrollment of some twenty students.

7. Annual meeting of external advisory council to provide guidance on the environmental graduate programs.

5.4.4 Department of Environmental Health Sciences (DEHS) - Education and Training Initiative

Project Director:	Janet Z. Temple, Ph.D.
Assistant Director	Mike Reed, CIH
Faculty	Robert Kennedy, Ph.D.
Faculty	William Hotle
Faculty	Nancy Kierstead
Administrative Specialist	Gerri Hollis
Accounting Technician	Paula Butler
Accounting Technician	Lisa Burkhardt

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.

Two Professional Development seminars were designed and developed during year two. The programs will be two days in length, and 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

A needs assessment instrument has been developed to secure profiles of mid and upper level managers and their training needs relating to risk. The product can be modified for application to other professions.

Milestones and Deliverables Achieved in Year 2

Planning/Administration

1. Hire key faculty to support Professional Development Series

   Dr. Robert Kennedy was hired July 6, 1993 to support Program Development. He has a Ph.D. in Epidemiology and a Masters of Science in Public Health concentrating in Occupational and Environmental Health. He most recently has been an Assistant Professor with Armstrong State College/Georgia Southern University in Epidemiology, Biostatistics, and Environmental Health at both the undergraduate and graduate level. Dr. Kennedy worked as an epidemiologist for the Agency for Toxic Substances and Disease Registry (ATSDR) in Atlanta developing a health surveillance system for workers employed in the remediation of hazardous waste sites. He also has worked as an Industrial Hygienist for a number of years with business and industry.

2. Networking to examine training needs of DOE facilities.
   A technical proposal and task plan has been submitted to the Office of Technology and Development to establish a demonstration project for the Professional Development Series in Risk.

   Conferences, seminars, and meetings attended by Dr. Jan Temple, Mike Reed , Dr. Robert Kennedy, Bill Hotle and/or Nancy Kierstead in Year 2 were:

   Michael O'Rear, Director of Solid Waste Division of DOE Savannah River Operations Office Friday, July 23, 1993 in Charleston, SC and August 19, 1993 in Aiken, S.C. to discuss education/training needs at WSRC.

   WSRC Environmental and Waste Management Information Exchange Forum August 30-31, 1993 in Augusta, GA. Held meetings with WSRC regarding Risk Management training.

   Hanford Summit conference meeting at Pasco, Washington, September 13-16, 1993. This was a national forum on environment, technology, and the economy. Served as one of the spokespersons for the Education and Training Task Force. Lunch with DOE Secretary O'Leary, Tom Grumbley, Governor Lowry and former governors, Daniel Evans and Booth Gardner.

   WSRC in Aiken August 30 & 31 with Site Risk Manager, Jeff Immel, and meeting with Julia Madden with WSRC Training Personnel in Aiken, September

1, 1993. Discussion addressed using WSRC as a demonstration site for the Professional Development series in Risk. Follow up with Tom Hindman on September 22.

Buddy Beck, Coleman Industry, regarding Risk agenda on, September 28.

Ken Koller, Idaho National Engineering Laboratory, September 29, regarding Risk training and a demonstration project at Idaho. Follow up discussion occurred November 2 & 3, 1993.

ER '93 Environmental Remediation Conference in Augusta, GA October 24-28.

Society for Risk Analysis Annual meeting December 5-8, 1993 in Savannah, GA.

Oak Ridge Associated Universities, Oak Ridge, TN. October 25-26. Dr Jan Temple is the Medical University of South Carolina counselor representative.

Mr. Max Lum of ATSDR Atlanta, GA on December 15, 1993 regarding Risk Analysis programs. A program in risk will be offered in 1994 by ATSDR at MUSC.

Dr. Bill Simpson and Dr. Robert Anderson November 1, 1993 to discuss Occupational health initiatives.

WSRC Environmental and Waste Management Information Exchange Forum in Aiken August 30 & 31. A proposal was submitted in response to the vendor fair meeting and is currently pending.

Hanford Summit II, Seattle, Washington January 20-22, 1994. Dr Jan Temple is a member of the Training and Education Committee.

American hospital Association Meeting, Lake Buena Vista, Florida, February 13-16. Dr. Jan Temple presented two programs.

"Risk Analysis Process in Environmental Decision Making
"EPA Regulatory Update"

March 12-16, 1994. National Environmental Information Association annual meeting, Mission Valley, California. "EM 94", March 12-16.

Presentation by Dr. Temple on Risk Communication
Presentation by Michael Reed and Jim Graves on Environmental Health

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.

ATSDR - Max Lum delivered 1 day Risk Communication course to MUSC June 2, 1994.

3. Other Presentations:
NC/SC Environmental Information Association meeting September 23, 1993 in Myrtle Beach, SC. A presentation, entitled "The Role of Risk in Environmental Health Issues", covered an overview of risk assessment, risk management, and risk communication. .

- Abstract submitted and accepted
  Slides from the presentation were used in the upcoming pilot test of the first Professional Development Seminar "Concepts of Risk Analysis" (71)

Fourth national Symposium and Trade Exhibition on Health Care Safety and the Environment, Orlando, Florida. A presentation, entitled "The Risk Analysis Process in Environmental Decision Making", covered an overview of risk assessment, risk management, and risk communication.

- Slides from the presentation were used in the upcoming pilot test of the second Professional Development Seminar "Decision Making in Environmental Risk Management" (72)

11th Annual Conference and Exposition of Environmental Information Association, San Diego, California. A presentation, entitled "Risk Analysis in Environmental Health Issues", covered an overview of risk assessment, risk management, and risk communication.

- Slides from the presentation were used in the upcoming pilot test of the second Professional Development Seminar "Decision Making in Environmental Risk Management" (73)

4. Medical Curriculum Research Committee established in consort with EHAP to undertake new education research initiatives. Dr. Jan Temple, Dr. Catherine Musham, Jan Bellack and Dylan Holmes will participate in meetings beginning the fourth quarter of fiscal year 1994.

5. In accordance with grant objectives, faculty reviewed the Federal Register on CD ROM as well as Internet and suggested Internet version be purchased. This was achieved through the MUSC main library information systems.

6. Continued to maintain an off-site library established to house environmental risk assessment, management and communication information

7 Supervised two interns during the month of July, 1993. They participated in the literature searches regarding 1)Ecological Risk Assessment and 2)Risk Management and Risk Communication. The information they collected will be valuable to future program development in these areas.

Advisory Committee

8. An advisory committee to support the professional training and education initiative convened November 3, 1993 and May 17, 1994 in Charleston SC. The advisory committee members reviewed the pilot presentation of the professional development series courses "Concepts of Risk Analysis" and "Decision Making in Environmental Risk Management." The advisory committee members provided valuable feedback and guidance on the course development and improvements to address state of the art risk analysis and management practices.

   - List of members serving on Advisory Committee (74)
   - Advisory Committee Meeting Minutes from November 3, 1993 (75)
   - Advisory Committee Meeting Minutes from May 17, 1994 (76)

9. An advisory committee handbook was created and describes the roles and functions of the committee

   - Handbook Revised November 1993 (77)

Needs Assessment Instrument

10. 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.

    - Revised survey instrument, developed in August, 1993 (78)

11. SCDHEC is discussing modification of the aforementioned survey instrument to secure profiles of nurse practitioners and environmental quality managers.

Program Design and Development

12. 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.

    A student textbook has been developed as well as slides for the lectures. The course was pilot tested to the advisory committee in November 1993. A second pilot test of the course was presented in Charleston Feb 1-2, 1994. Members of both EHAP, MUSC, and the Department of Energy, Savannah River Site attended the February seminar.
    - Concepts of Risk Analysis Textbook (79)

13. Course development for the second Professional Development Seminar entitled "Decision Making in Environmental Risk Management" is nearing completion. 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. A student textbook has been developed as well as slides for the lectures. The course was pilot tested to the advisory committee May 17 - 19, 1994. A second pilot presentation of the course is scheduled for August 1994.

- Decision Making in Environmental Risk Management Textbook (80)

14. Literature searches are underway to obtain information for the development of the next two courses in the professional development series: Risk Communication and Executive Overview of Risk Analysis.

15. 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 Concepts of Risk Analysis and Ecological Toxicology. Trained 28 engineers as part of base closure reeducation process. Phase one course offering ran June 6-June 29, 1994. A second phase of courses will be offered in August.

- Course agenda (81)

Academic Initiative

16. Curriculum Development
The Department of Environmental Health Sciences developed and submitted a draft curriculum for a track in Environmental Health Sciences within the Environmental Studies Graduate Program. Status pending.

17. National Search
A national search was conducted for an Academic Program Director for the Department of Environmental Health Sciences. Two department faculty members participated on the search committee and in interviews with prospective candidates. Dr. Nurtran Esmen was the candidate of choice. Due to funding limitations the position was not filled.

Milestones and Deliverables Planned for Year 3

Planning/Administration

1. Networking & meetings planned for next year July 1, 1994 - June 30 1995.

TAPPI Research Management Committee. Committee member, Dr. Jan Temple.

Charleston Naval Base Reuse Higher Education Consortium.

WSRC to finalize Risk Education and Training Programs.

- National Association of Environmental Professionals: Development of Academic Centers.

Needs Assessment Instrument

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

3. Meet with SCDHEC, Lillian Mood/Steve Richardson, to develop assessment instrument to secure data on nurse practitioners and environmental quality managers.

Advisory Committee

4. The advisory committee is scheduled to hold meeting in November 1994 and May 1995. Members of the committee will be invited to attend the initial pilot testing of the third Professional Development Seminar on Risk Communication - November 9 & 10, 1994.

    - Minutes of Advisory Board Meetings

Program Design and Development

5. Course development for the second Professional Development "Decision Making in Environmental Risk Management" will be completed after a second review of materials by the advisory committee.

    - Deliverables will include the agenda, student handbook, slides and other audio visual aids, course examination, and course evaluation.

6. Course development for the third Professional Development seminar "Risk Communication" will be conducted and the course will be pilot tested to the advisory committee.

    - Deliverables will include the agenda, student handbook, slides and other audio visual aids.

7. Course development will begin for the fourth Professional Development seminar, "Executive Overview of Risk Assessment." The course will be pilot tested for the advisory committee in the May 1995.

    - Deliverables will include the agenda, student handbook, slides and other audio visual aids.

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