DOE/EW/50625--T23

ENVIRONMENTAL HAZARDS ASSESSMENT PROGRAM
ANNUAL REPORT
July 1, 1994 -- June 30, 1995

FOR

GRANT DE-FG01-92EW50625

SUBMITTED TO THE
U. S. DEPARTMENT OF ENERGY

BY THE

MEDICAL UNIVERSITY OF SOUTH CAROLINA

July 31, 1995

Annual Highlights

- On April 1, Lawrence C. Mohr, Jr., M.D. became the new director of EHAP. Dr. Mohr has a long and distinguished career in medicine and in the military and his presence as director is enhancing the Program's ability to involve health-care providers. Dr. Mohr maintains an active clinical practice, bringing day-to-day physician experience to the Program.

- In the Science Programs section, two new projects related to TCE have begun. One is directed by James S. Norris, Ph.D., and its title is "Real-Time Measurement of Oxidative Free Radical Generation and Quantification of DNA Damage in the Same Cells." Dr. Norris and other experienced researchers seek to determine whether TCE or its metabolites induce free radical generation in the peroxisomes of established and primary human liver cells as primary cultures.

- "Immunogenetic Epidemiology of Scleroderma," is directed by Janardan P. Pandey, Ph.D. As the title suggests, Dr. Pandey is conducting a case-control study to ascertain the real relationship between scleroderma and environmental exposure to TCE.

- Harold May, Ph.D., is leading the project "Anaerobic Dechlorination of Polychlorinated Biphenyls (PCBs) and the Biodegradation of Ether-Containing Gasoline Additives and Ether Solvents," which has made significant progress regarding future remediation efforts. Anaerobic dechlorination of PCBs in essence detoxifies a contaminated site. *Ortho* dechlorination is very rare and has only been reported twice. In both of the reported cases, the activity was very slow in development (6-12 months) and was not sustained. Dr. May's enrichment showed activity in five weeks and has been sustainable. Again, attack of the *ortho* positioned chlorines is rare, and hence, the characterization and development of this type of dechlorination could be of use in future remediation efforts.

- Dr. Frank Parker, chairman of the External Advisory Group (EAG), delivered the Group's report in early February. The document serves as a blueprint for strengthening the Program.

- The Information Systems group and other EHAP sections integrated their respective capabilities to implement and bring on-line the EHAP World Wide Web (WWW) Server. EHAP's Web page is available to all those on the Internet, and among other purposes, it serves as a means to educate the public about environmental health at MUSC, other universities and governmental agencies.

- Dr. Daniel T. Lackland presented "Geo-coding of Health and Demographic Data as a Resource for Environmental Incidents Preparedness and Response" at the American Nuclear Society Topical Meeting: Emergency Preparedness and Response, April 19-21 in Savannah, GA.

- In collaboration with Coleman Research Corporation (CRC) and the Atomic Energy Authority Technology Consultancy Services (AEA) of the United Kingdom, we are preparing the "Risk Assessment/Risk Management International Symposium Study." This project is designed to examine environmental risk assessment and risk management practices in the United States and in UK/Euro·/International.

- Dr. David G. Hoel continued to act as project director for the International Risk Assessment/Risk Management Forum. In this role, Dr. Hoel serves as primary liaison between the Medical University, the U.S. Department of Energy and the project's Steering Committee.

- Crossroads' community intervention project in Blackville, SC successfully continued to increase environmental health awareness within this community located near the U.S. Department of Energy Savannah River Site. An essay contest for all Blackville elementary, middle and high school students and a Barnwell County Chamber of Commerce After Hours Event were held in April and May.

- Moreover, as part of MUSC/EHAP's leading partnership role, Crossroads has started to develop of a comprehensive, long-term plan for the Charleston Enterprise Community (EC). This plan is called the Healthy Community Initiative and may serve as a model for other communities across the country.

- On June 1, Dr. David Jollow and Dr. David G. Hoel received the final copy of ChemRisk's report, which was first presented at the Trichloroethylene (TCE) Data Analysis Project peer review March 23-24 in Charleston. This was a cooperative effort among MUSC, Coleman Research Corporation, Cammer and Associates and ChemRisk Division of McLaren/Hart Environmental Engineering Corporation to produce an independent analysis for consideration in establishing safe clean-up levels of TCE. As a result of this project, Dr. Hoel has requested funding for a project that begins with a follow-up of the results of the PBPK work of ChemRisk and the Peer Review Panel. The project will work towards developing a risk model for low-dose exposures to TCE.

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1.0 INTRODUCTION

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

Dr. James B. Edwards, President of the Medical University of South Carolina suggested, "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 Thomas Jefferson's quotation.

> "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 to expand the base of environmental knowledge. Moreover, it is appropriate that an educational institution such as MUSC utilize this information to help people from all walks of life understand better what truly does affect human health, what does not, and why.

Note
In the case of text enclosed by a dotted border, such as this example, this represents an effort funded by other sources in support of the total EHAP mission. Moreover, this border means no grant funds were expended in creating the project.

Grant Objectives

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

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

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

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

This report describes activities and reports on progress for the third 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 Susan G. Legare in the EHAP office of the Medical University of South Carolina at (803) 727-6450.

2.0 PROGRAM OVERVIEW

2.1 Program Elements

As the program has evolved, more projects have been funded and many existing projects have become more complex. Thus, to accomplish better the objectives over the years and retain a solid focus on the total mission, we have reorganized the grant effort from three to five major elements: 1) Public and Professional Outreach; 2) Clinical Programs; 3) Science Programs; 4) Information Systems; and 5) Program Management.

The relationship of these elements among each other is shown in Figure 2.0. Each element has a specific programmatic function 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.

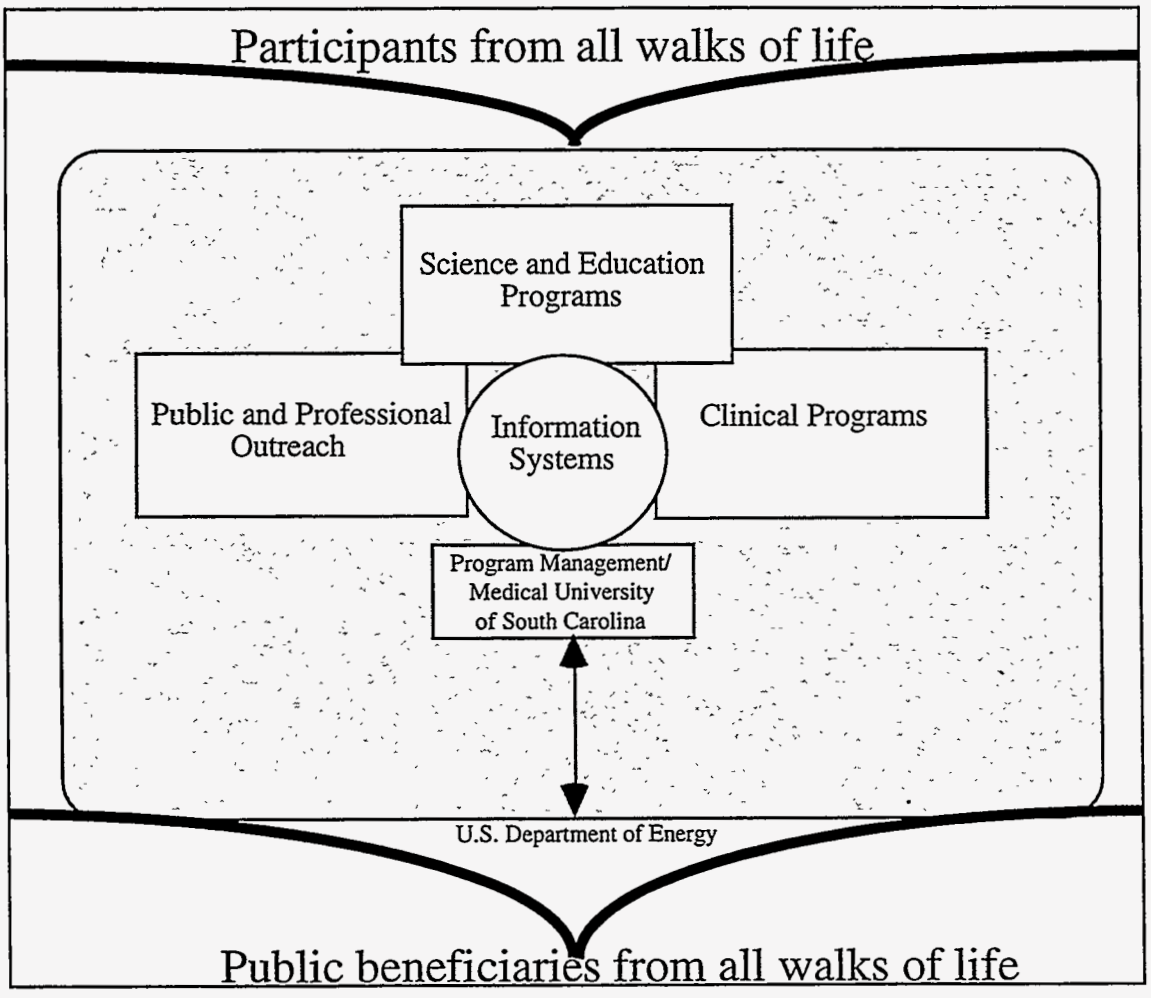

Figure 2.0. The Major Program Elements and Their Relationships.

During the third year and under the category of Public and Professional Outreach, we continued our successful Crossroads of Humanity Series. In this Series we bring the pool of experts and results developed in our workshops and round table forums to bear on real problems. Hence, we have moved from the hypothetical to the actual, with the basis focused on human health. Additionally, mid- and upper-level managers are being trained in risk assessment to ensure those decision-makers in the environmental cleanup business are better informed.

The focus on human health has continued in the Clinical Programs section wherein research on the management of hazardous waste is being undertaken and synthesized from a range of sources. Results of this research and other studies of risk assessment are woven into the diagnostic backgrounds of established general practitioners; this continuing education program increases the risk assessment capacity of many physicians.

Science Programs provide a foundation to enable health care providers and researchers to deeply explore environmental health issues. Focusing on trichloroethylene research, the Science element continues work on numerous research projects that are initially providing some of the hard facts needed to assess certain environmental health risks. 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.

To ensure we accomplish the grant objectives in an effective and efficient manner, the Program Management element provides reporting, budgeting, and accounting as well as monitoring and program direction to those actively involved in EHAP initiatives. The Program Management group is 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.

Interwoven throughout EHAP, the Information Systems section provides and maintains the computer and network structure for information handling. Moreover, Information Systems continues to work to refine the data fusion techniques necessary to provide the user with advanced, user-friendly information search and retrieval capabilities.

2.2 Program Expenditures

The following presents an overview of estimated Year 03 grant expenditures and total expenditures since the grant's inception.

	Year 3	Total
	(Dollars in thousands)	
Public and Professional Outreach Crossroads of Humanity Series Publications/Information Research and Evaluation Professional Training	$1,213	$3,564
Science Programs Toxicology Risk Assessment Education	$2,007	$4,457
Clinical Programs Health Services Research Family Medicine	$484	$647
Information Systems	$1,288	$2,932
Indirect Costs	$1,962	$4,644
Equipment	$198	$1,127
Total	$ 7,152	$17,371

At the time this report was printed, all expenditures related to Year 03 had not been made. MUSC has until August 31, 1995, to file a final invoice with DOE. The Year 03 award is $7,302,882. Obligated funds for the year ended June 30, 1995, are $7,152,238. All obligated funds for Year 03 will be expended in support of grant initiatives.

3.0 PROGRAM MANAGEMENT

The MUSC administration established the Environmental Hazards Assessment Program Office 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 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 President. To support this office, MUSC has made non-federal funds available to the director.

Principal Investigator:	James B. Edwards, D.M.D.
Executive Assistant to Principal Investigator:	Steven L. Jones, B.S., M.S.W.
Deputy Principal Investigator and Director:	Lawrence C. Mohr, Jr., M.D.
Director of Development:	R. Martin Jones, Ph.D.
Assistant to Director for Operations:	Jack C. Davis, M.S.
Assistant to Director for University Programs:	W. Allen Smith, DR., P.H.
Assistant to Director for External Programs:	Robert Draughn, D.SC.
Assistant to Director for Administration and Finance:	Susan G. Legare, B.S., C.P.A.
Director for Crossroads:	Glenn A. Fleming, Ed.D.
Director for Research, Science and Education:	Rosalie K. Crouch, Ph.D.
Business Manager:	Gail C. Brubaker
Assistant Project Administrator:	Marion H. Watson
Project Administrator:	Charles W. Waring, III
Administrative Assistant:	Jill Canaday
Administrative Specialist:	Mimi Gainey
Accounting Technician:	Anita G. Noisette

Milestones and Products for Year 3

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

1. Grant funding enabled MUSC to hire two environmental microbiologists whose research efforts will be directed in the areas of dioxin and PCBs. In addition, they will support the education

initiatives in the new Masters of Environmental Studies Program jointly offered by MUSC and the University of Charleston.

2. AEA Technology Consultancy Services (AEA) delivered its final reports on the subject of the development of an overall framework for risk-based decision making with respect to land use. The project began in April 1994, and was completed September 30 with the delivery of the reports.

   - AEA Report (1)

3. Interactions with respect to collaborative programs have continued with INEL. Through this relationship, we made initial contact with Metrica Corporation, which is a minority-owned company located in San Antonio, Texas. It is actively involved in environmental programs with the U.S. Air Force.

4. Involvement in environmental programs by faculty of the MUSC College of Dental Medicine has increased. A team of dental faculty has been formed to develop instructional materials concerning environmental issues of importance to dentists. The team consists of: W.E. Burton, D.D.S., J.M. Barry, D.D.S., F.A. Young, D.Sc., and R.A. Draughn, D.Sc. In collaboration with EHAP Assistant Professor, Dr. Catherine Musham, a survey document was designed to determine attitudes and activities relative to teaching in the area of environmental issues associated with clinical materials used by dentists. The survey will be distributed to the directors of all dental general practice residencies in the U.S. Information from the survey will be used as preliminary data to support the definition of a plan for the development of instructional materials. The preparation of a manuscript on our study of attitudes and activities toward environmental issues in general dentistry residency training programs neared completion. A draft manuscript was prepared and will continue to be reviewed and revised through the next year.

5. Partnerships with Clark Atlanta University in Atlanta, GA, were initiated. Clark Atlanta University (CAU) is a historically black university with a long history of education, outreach, service, and technical assistance to underrepresented populations and communities. EHAP seeks input from CAU's Environmental Justice Resource Center, which is very interested in participating in a Crossroads of Humanity Series forum concerning environmental risk in an urban/industrialized area. The time and place of this forum are currently being planned.

6. With consulting services provided by Dr. Glenn Fleming and his staff, INEL's Buried Waste Integrated Demonstration Program presented its public outreach forum in November. This is the first export of the public outreach program designed and developed by EHAP. This collaborative effort is a direct outgrowth of the expertise developed by the Crossroads Series in public and professional outgrowth through its various round tables, workshops and town meetings.

7. The External Advisory Group met November 21-22 in Charleston to review the program and provide guidance for future initiatives. Each of the seven members brought a broad professional background, demonstrated expertise and international reputation to bear on the review process. Dr. Frank Parker, the chairman of the External Advisory Group (EAG), delivered the Group's report in early February. Planning for the July meeting of the EAG was initiated.

   - Copy of report (2)

8. Mr. David E. Rivers was hired as a new research associate in January. Mr. Rivers is very experienced in outreach, community planning, public policy and management and will work in two basic areas--Public and Professional Outreach and Development.

9. In collaboration with Coleman Research Corporation (CRC) and the Atomic Energy Authority Technology Consultancy Services (AEA) of the United Kingdom, we are preparing the "Risk Assessment/Risk Management International Symposium Study." This project is designed to examine environmental risk assessment and risk management practices in the United States and in UK/Europe/International, comparing and contrasting approaches and involving a wide range of stakeholders through reports, workshops, an International Forum and Steering Committee evaluations.

10. We began first draft of a program review of EHAP, projecting the activities of each project throughout the life of the grant.

11. Contact was made with staff of the Brookhaven National Laboratory regarding collaboration in the area of teaching of risk assessment and risk communication.

12. In the Science Programs section, two new projects related to TCE have begun. One is directed by James S. Norris, Ph.D., and its title is "Real-Time Measurement of Oxidative Free Radical Generation and Quantification of DNA Damage in the Same Cells." Dr. Norris and other experienced researchers seek to determine whether TCE or its

metabolites induce free radical generation in the peroxisomes of established and primary human liver cells as primary cultures.

13. Another new project is led by Janardan Pandey, Ph.D., Richard M. Silver, M.D., and Susan Sutherland, Ph.D., and it is entitled "Immunogenetic Epidemiology of Scleroderma." As the title suggests, the project team is conducting a case-control study to ascertain the real relationship between scleroderma and environmental exposure to TCE. Because Dr. Silver has over 400 case studies of scleroderma at MUSC, he expects to be able to take advantage of the University's ongoing efforts in finding answers to questions regarding human health.

14. We held strategic planning sessions to seek options and to find answers dealing with what EHAP will do when the original grant funding expires.

15. The TCE Data Analysis Project was approved for funding in August. This is a cooperative effort among MUSC, Coleman Research Corporation, Cammer & Associates and ChemRisk Division of McLaren/Hart Environmental Engineering Corporation to produce an independent analysis for consideration in establishing safe clean-up levels of TCE. Dr. David G. Hoel and Dr. David Jollow of MUSC will co-chair the peer review panel. A prospective list of ten panelists was approved, and we received preliminary acceptances from all ten members. Dr. Hoel and Dr. Jollow hosted the TCE Data Analysis Project peer review, which was held March 23-24, in Charleston. A preliminary report was presented by ChemRisk and discussed by the panel of distinguished scientists. Later, a final report was issued.

    - Copy of report (3)

16. On April 1, Lawrence C. Mohr, Jr., M.D. became the new director of EHAP. Dr. Mohr has a long and distinguished career in medicine and in the military and his presence as director is enhancing the Program's ability to involve health-care providers. Dr. Mohr maintains an active clinical practice, bringing day-to-day physician experience to the Program. R. Martin Jones, Ph.D., former director of EHAP, remains active in EHAP as the director of development as well as remaining an active contributor on grant efforts in education, research and outreach.

Milestones and Products Projected for Year 4

1. We will host a symposium, "The Environmental Risk Assessment--Does it Work for the Family Physician?" October 26-27. MUSC's Department of Family Medicine and EHAP will sponsor this event,

which is being convened because there is the believe that the risk assessment process, as it is currently practiced, does not result in a usable or useful product for the practicing physician. As a result of the meeting, we expect to increase physician participation in the environmental health risk dialogue.

2. EHAP's External Advisory Group (EAG) will meet in Charleston July 24-25. Among other charges, the EAG will make recommendations to the Principal Investigator on how the Program can best proceed in the future to meet current objectives and new goals.

3. In collaboration with Coleman Research Corporation (CRC) and the Atomic Energy Authority Technology Consultancy Services (AEA) of the United Kingdom, we will continue to prepare the "Risk Assessment/Risk Management International Symposium Study." The symposium is planned for April 1996.

4. We will continue to hold strategic planning sessions to seek options and to find answers dealing with what EHAP will do when the original grant funding expires.

5. To continue the efforts started under the grant, Lawrence C. Mohr, Jr., M.D., will coordinate a study on establishing an institution such as a Center for Environmental Studies or a College of Environmental Health Studies at MUSC.

6 We will seek to hold a Risk Visionary conference in the spring of 1996. The purpose would be to discuss and attempt to find answers to questions about current risk reform legislation.

4.0 PUBLIC AND PROFESSIONAL OUTREACH

4.1 Crossroads

Executive Summary

During the third year, Public and Professional Outreach built upon the work and planning of the second year in a manner 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.

As the Public and Professional Outreach initiative has evolved, its focus has narrowed from broad, hypothetical issues and formats (such as the Socratic dialogues, *In Search of Purity* and *Purity Revisited*, circa 1993) to specific, "real-world" settings. Year 3 activities reflect this shift. Significant efforts during the year included development and implementation of Research and Evaluation programs in Cassatt, Blackville and Charleston, SC. The Blackville and Charleston Neck Area projects are ongoing.

Public and Professional Outreach staff devoted part of Year 3 activities to development of the kind of multi-disciplinary partnerships necessary to develop and implement successful programs relating to environmental health risk issues. During Year 3, MUSC/EHAP served in a consultancy role in production of a dialogue on environmental risk for the Idaho National Engineering Laboratory's Buried Waste Integrated Demonstration (INEL/BWID). During the Fourth Quarter of Year 3, MUSC/EHAP entered into a partnership with the City of Charleston for development of a comprehensive Healthy Community Initiative for the aforementioned Charleston Neck area, parts of which have been designated an Enterprise Community by the U.S. Department of Housing and Urban Development. Another promising partnership discussed during Year 3 includes possible teaming between MUSC/EHAP and Albright & Wilson of the Americas, Inc., a chemical manufacturing company located in the Charleston Neck area. A significant risk assessment/public outreach effort may result during Year 4.

Also, MUSC/EHAP and the MUSC Department of Family Medicine began the planning process for a two-day symposium entitled, "The Environmental Risk Assessment -- Does It Work for the Community-Based Family Physician?" scheduled for October 26-27, 1995, in Charleston. This program will stimulate interest and encourage greater participation among the primary care medical community in the discussion and resolution of environmental risk issues. Participants will evaluate the utility of the current risk assessment process to family practice physicians in their role as a community health advocates, then explore methods of improving this utility.

Crossroads staff continued publication and information efforts in support of MUSC/EHAP. These include: the EHAP newsletter (*EHAP News & Information*); ongoing development of the Crossroads Series database; publication support of MUSC's graduate-level programs in Risk Assessment and Environmental Studies; publication and logistical support of Research and Evaluation efforts in Blackville, SC; publication support of EHAP Program Management activities; publication and logistical support of the MUSC-EHAP External Advisory Group, and publication and logistical support of the International Risk Assessment/Risk Management Forum.

Objectives

1. To perform research in areas of risk perception and risk communication.

2. To develop and implement productive partnerships affecting the overall environmental health of real communities, such as Cassatt and Blackville, SC, and the Charleston (SC) Neck area.

3. To develop partnerships with governmental and corporate entities, such as INEL/BWID and Albright & Wilson, with positive effects on stakeholders' environmental knowledge and health.

4. To continue development of programs relevant to the relationship between family medical practitioners and the environmental risk assessment community.

5. To publish printed materials related to EHAP and the Crossroads Series.

6. To publish material and provide information and logistical support for Program Management, Science, Education and Information Systems initiatives.

7. To maintain and develop the Crossroads Series database.

4.1.1 Crossroads of Humanity Series	
Director:	Glenn A. Fleming, Ed.D.
Events Coordinator:	Sylvia Rivers
Administrative Assistant:	Percilla Coaxum

Milestones and Products for Year 3

Inaugurated Blackville Project described in above introductory overview segment of Crossroads Series quarterly report. Completed Phase I of project. Implemented Phase II of project.

1. Created a Blackville Project Committee at MUSC.

2. Published a Blackville Project Proposal.

   - Copy of proposal (4)

3. Established a Citizens Steering Committee in Blackville and held two meetings.

   - Minutes of meetings (5)

4. Surveyed and secured site for Blackville Environmental Health Issues discussion.

5. Developed videotape production plan with SCETV in November.

6. Planned telephone surveys of Blackville citizens.

7. Hired Ms. Mildred Ford as MUSC Community Liaison in Blackville.

8. Planned "Clues to Unraveling the Association Between Illness and Environmental Exposure," March 1995, in Greenville, SC. This workshop was designed for nurses working in community, occupational, primary care and other health care settings. Co-sponsors included the Agency for Toxic Substances and Disease Registry (ATSDR) and the South Carolina Department of Health and Environmental Control (DHEC). (7-12/94)

9. Continued discussions with DHEC (Lil Mood) and the University of South Carolina College of Nursing regarding project in Cassatt, SC. (7-12/94)

10. Participated in planning for statewide conference on environmental justice. (7-9/94)

11. Continued to overhaul the Crossroads of Humanity database, adding experts as they were identified. This effort is ongoing so as to provide user-friendly access to the data critical for networking. Effective end of Year 3, Database contained 3,506 entries.

12. Planned transition of Crossroads Series database to new program, enabling more efficient storage and recall of prospective experts and audience members.

13. Met with representatives of INEL, who held a Socratic dialogue on radioactive and hazardous waste remediation on November 19, 1994 in Idaho Falls, ID. (7/26-28 and 9/7-9) Three future meetings were scheduled during Year 3, Quarter 1.

14. Conducted meetings of Blackville Citizens Steering Committee.

15. Conducted and videotaped first Blackville Environmental Health Issues Discussion (11/1/94). Dr. Glenn Fleming moderated a question-and-answer format, exploring community environmental health issues with 12 citizen-panelists.

    - BEHID program brochure (6)
    - Clip file of related newspaper articles and advertisements (7)
    - BEHID press releases (8)
    - BEHID poster (9)
    - Blackville Environmental Health Issues Discussion (BEHID) videotape (10)

16. Planned community-wide circulation of BEHID videotape in conjunction with Blackville-EHAP Community liaison Mildred Ford and Blackville Citizens Steering Committee (11/12/94).

17. Continued development of discipline-specific "blue ribbon" panels including physicians discussing risk assessment information, and mayors and first response individuals. The purpose of these future panels is to address issues identified in previous Crossroads Series round table forums and workshops. (9-12/94).

18. Assisted INEL's Buried Waste Integrated Demonstration (INEL BWID) in production of a Socratic dialogue on buried waste issues, conducted 11/19/94 in Idaho Falls, ID. Twelve panelists role-played a hypothetical scenario, which was videotaped for later television broadcast. Final program editing will be completed during Third Quarter, Year 3.

19 Circulated 500 videos of the November 1994 BEHID. Created video packages and new posters for display in high traffic areas in Blackville.

20. Attended several organizational meetings, including the civic club, town council and church meetings, to present the BEHID video and to discuss the Blackville-MUSC partnership and environmental health concerns.

21. Arranged and sponsored the Barnwell County Chamber of Commerce April Business After Hours Reception. This event promoted the BEHID video to community business leaders. It also informed those attending of speakers who will deliver environmental health presentations within the Blackville community.

22. Developed news releases and public service announcements about the BEHID video detailing how to obtain them.

    - Copy of news releases and copies of public service announcements (11)

23. Created a Blackville Community Newsletter called "Enviromation," which discusses the MUSC-Blackville Partnership, the BEHID video and other MUSC/EHAP/Blackville events. This newsletter continually updates the citizens on the project's progress and provides them with environmental health information and education.

    - Copy of newsletter (12)

24. Conducted regular visits to Blackville to continue developing community efforts for environmental health promotion and discussion.

25. Arranged for students in grades 4-12 in Blackville public schools to view the BEHID video. Conducted an essay contest -- "How I can Improve the Environment in Blackville"--in these grades to promote discussion and education of environmental health issues. 205 students submitted essays. The top three were chosen in three categories: elementary, middle and high school levels. Cash prizes and plagues were awarded.

- Copies of winning essays (13)

26. Conducted and/or attended meetings related to development of a Blackville-style initiative in an urban-industrial community.

27. Met with Dr. Robert Bullard and Mr. Delane Garner of Clark Atlanta University regarding environmental equity issues in urban-industrial communities such as the "Neck" area of the Charleston peninsula.

28. Attended introductory and question-and-answer sessions regarding federal government designation of portions of the City of Charleston, and contiguous, unincorporated areas of Charleston County as an Enterprise Community (EC).

29. Attended meeting at Charleston City Hall for the purpose of city officials' announcement of EC designation for portions of the city, including the Neck area. MUSC/EHAP attendees were Mr. David Rivers and Mr. Richard Jablonski. Also attending were Charleston Mayor Joseph P. Riley Jr., U.S. Congressman James Clyburn, and representatives of U.S. Senator Ernest Hollings and the U.S. Department of Housing and Urban Development (HUD) (3/27/95).

30. Continued ongoing series of meetings between Mr. Rivers of MUSC/EHAP and federal, state and local officials, including representatives of HUD and the U.S. Department of Health and Human Services. Contacted and obtained EC application documents from officials in Charlotte, NC; Philadelphia, PA/Camden, NJ; and Birmingham, AL (4-6/95).

31. Attended additional meeting at Charleston (SC) City Hall for purpose of discussing the Medical University's role as a major partner in applicat. ı of a Healthy Community Initiative in the Charleston EC. Those in attendance included Mayor Riley and Ms. Patricia Crawford of the City of Charleston; Congressman Clyburn and Mr. Davis Marshall from his staff; and Dr. Lawrence Mohr, Mr. Rivers and Mr. Jablonski from MUSC/EHAP (6/5/95).

32. Conducted and/or attended meetings related to development of a partnership between the Medical University and Albright & Wilson of the Americas. Such a partnership may include scientific review of an environmental risk assessment of Albright & Wilson activities, followed by public outreach activities in potentially affected communities.

33. Conducted meeting at MUSC/EHAP offices to discuss potential partnership between EHAP and Albright & Wilson. Meeting attended by Mr. Bill Helfenstein, Mr. John Stoney and Mr. Moses Clarkson of Albright & Wilson, and Dr. Mohr, Dr. Glenn Fleming, Ms. Susan Legare and Mr. Jablonski of MUSC/EHAP (6/22/95).

34. Attended follow-up meeting at Albright & Wilson plant. Meeting attended by Mr. Helfenstein, Mr. Stoney and Mr. Clarkson of Albright & Wilson, and Mr. Jablonski of MUSC/EHAP (6/26/95).

35. Assisted Idaho National Engineering Laboratory's Buried Waste Integrated Demonstration (INEL BWID) in circulation of a Socratic dialogue on buried waste issues, conducted 11/19/94 in Idaho Falls, ID. Twelve panelists role-played a hypothetical scenario, which was videotaped for later television broadcast. The final version of the program was made available to interested stations, via satellite feed, 6/4/95. Among those institutions expressing interest in airing the INEL BWID Socratic dialogue is Francis Marion University in Florence, SC. Through its Cauthen Media Center, Francis Marion University tentatively plans to make the program available to 28,000 cable television subscribers in the South Carolina Pee Dee region.

Milestones and Products Projected for Year 4

1. Will complete and report on the Blackville project.

2. Will co-sponsor "The Environmental Risk Assessment -- Does It Work for the Community-Based Family Physician?" scheduled for October 26-27, 1995, in Charleston, SC.

    - White Paper on symposium

3. Will coordinate development of a comprehensive, long-term plan for the Charleston Enterprise Community (EC). Plan will be known as the Healthy Community Initiative and may serve as a model for other communities across the country.

4. Will explore partnership possibilities with Albright & Wilson Americas, Inc., for the purpose of review and outreach effort of the company's latest model environmental risk assessment.

4.1.2 Research and Evaluation	
Research Director:	Catherine Musham, Ph.D.
Research Associate:	Dylan Holmes

Milestones and Products for Year 3

1. Two studies were accepted for presentation at the Society for Risk Analysis annual meeting (Baltimore, MD, December 1994). One study concerned childhood lead poisoning health promotion focus groups, and the other is about medical educators' perceptions of environmental health curriculum. (7/94)

   - Acceptance letter (14)
   - Abstract 1A (15)
   - Abstract 1B (16)

2. Submitted two papers on the findings of the comprehensive study of medical educators' perceptions of environmental health curriculum study. Papers submitted to Family Medicine, and Journal of Nursing Education. (7/94)

   - Copy of paper 2A, Musham, et al. (17)
   - Copy of paper 2B, Bellack, et al. (18)

3. Attended monthly South Carolina Family Practice Research Consortium meetings for continued support of environmental risk perception and communication research.

   - Meeting Minutes (19)

4. Kimberly Doctor, an undergraduate student at South Carolina State University joined the research division as a summer intern under the direction of Dylan Holmes. Ms. Doctor worked on several research projects including the childhood lead poisoning focus group study. (7-8/94)

5. Formed a new research group focusing on the study of environmental education for dental professionals. Members include: William Barton, D.D.M., Robert Draughn, Ph.D., Catherine Musham, Ph.D., Dylan Holmes, B.B.A. (8/94)

6. Janet Holdsworth, a graduate student at the University of Charleston joined the research division as an intern and worked under the direction of Catherine Musham, Ph.D., on several research projects. (8/94)

7. Developed a survey instrument measuring the environmental health knowledge level and educational needs of citizens' advisory committees.

    - Survey instrument (20)

8. Catherine Musham, Ph.D., and Glenn Fleming, Ed.D., invited an environmental risk researcher, Abe Wandersman, Ph.D. (University of South Carolina) to join the research division as an advisor and active participant in research projects. Invitation accepted. (9/94)

    - Appointment proposal (21)

10. Developed an outline for research to be conducted as part of the Blackville project. Outline approved by project's steering committee.

    - Project timeline (22)

11. Conducted an evaluation of a training workshop, co-sponsored by the Office of Continuing Education, the MUSC College of Nursing, and EHAP, entitled "Clues to Unraveling the Association Between Illness and Environmental Exposure." (9/94)

    - Survey instrument (23)

    - Result summary (24)

12. Catherine Musham, Ph.D. is serving on dissertation committee evaluating work proposed by Mr. Michael K. Pisarck, MUSC Department of Biometry and Epidemiology.

    - Research proposal (25)

13. Prepared and distributed a report of the evaluation of the Crossroads Series Town Meeting. (9/94)

    - Evaluation report (26)

14. To measure dental educators' perceptions about the need for environmental health education in dental training programs, a written survey was administered to national general practice dental residency

directors and the directors of advanced education general dentistry programs. Co-authors Catherine Musham, Ph.D., Dylan Holmes, B.B.A., William Burton, D.D.M., and Robert Draughn, D.SC. created "A Survey of Dental Educators Perceptions about Environmental Health Education" (10/94).

- Survey instrument (27)

15. Received a total of 170 returned surveys (response rate =77%), analyzed the data using SPSS, and compiled a listing of open-ended responses for "A Survey of Dental Educators Perceptions about Environmental Health Education" (12/94).

16. To measure family physicians' attitudes and behaviors regarding disseminating environmental and lifestyle health risk information to their patients, a written survey was administered to a random selection of practicing family physicians in South Carolina (n=500). Co-authors Catherine Musham, Ph.D., Janet Holdsworth, M.P.A., and Dylan Holmes, B.B.A., created "Family Physicians' Attitudes Toward Providing Patients with Environmental and Lifestyle Health Risk Communication." This research was supported by the South Carolina Family Practice Research Consortium (11-12/94).

- Survey instrument (28)
- Preliminary paper draft (29)

17. Revised and updated a preliminary research proposal to investigate perceptions about environmental health risks of citizens in Blackville, SC.

18. Conducted focus group studies to evaluate the current environmental perceptions of residents in Blackville, SC.

- Focus group topic outline (30)
- Focus group recruitment posters (31)
- Focus group transcripts (32)

19. Designed and implemented a telephone survey of Blackville citizens to assess baseline community knowledge of environmental health topics.

- Survey instrument (33)
- Aggregate results (34)

- Telephone survey and focus groups summary report (35)

20. Presented preliminary results of a completed pilot study of lead poisoning education materials distributed in Charleston low income/minority communities at the Society for Risk Analysis annual meeting, December 4-7, 1994. This study used focus groups to better understand the perceptions of mothers of children at risk about childhood lead poisoning prevention education. Co-authors were Catherine Musham, Ph.D. and Dylan Holmes, B.B.A.

    - Poster illustration (36)

    - Abstract (37)

    - Program itinerary (38)

21. Presented results of the "Medical Educators' Attitudes Toward Environmental Health Education" study of three groups of medical educators (medical school academic deans, directors of nurse practitioner programs and directors of family practice residency programs) about the need for environmental health education at the Society for Risk Analysis annual meeting, December 4-7, 1994. This study involved three separate written surveys of national samples of educators in the three categories. Co-authors were Catherine Musham, Ph.D., Jan Bellack, Ph.D., David Graber, Ph.D., and Dylan Holmes, B.B.A.

    - Presentation slide illustrations (39)

22. Prepared "Family Practice Educators' Environmental Health Expectations" for publication in the Journal of Family Medicine. Co-authors were Catherine Musham, Ph.D., Jan Bellack, Ph.D., David Graber, Ph.D., and Dylan Holmes, B.B.A.

    - Paper to be submitted (40)

23. Dr. Abe Wandersman received approval as a consultant to the Crossroads Research and Evaluation division (12/94).

    - Dr. Wandersman's Curriculum Vitae (41)

24. Developed a structured environmental research intern program for undergraduate students.

    - Preliminary intern program proposal (42)

25. Completed analysis of dental educator survey assessing dental educators' perceptions regarding the need for environmental health education in graduate school.

    - Dental paper draft (43)

26. Received favorable notice from Dr. Barry Weiss, editor of Family Medicine, on the submitted manuscript, "Environmental Health Training in Family Practice Residency: A Survey of Program Directors." Dr. Weiss recommended a few changes before publication. These changes have been made and a revised copy has been sent to him.

    - Revised manuscript (44)

27. Developed proposal for an environmental health topics in undergraduate engineering schools study with Dr. Janet Z. Temple of MUSC's Department of Environmental Health Sciences.

    - Sample population listing (45)

28. Finalized survey instrument and protocol for the study of stakeholder perspectives in two South Carolina communities with Dr. Abe Wandersman of the University of South Carolina's Department of Psychology.

29. Tested feasibility of using the Crossroads "Purity" Round table videotapes as educational tools. Two tape viewings and subsequent focus group discussions were conducted in two graduate-level classes (Department of Medicine and Department of Marine Biology, USC). Presently a proposal is being developed to examine educational uses of the "Purity" tape in a wide range of class levels, from junior high through graduate training.

30. Submitted the following three abstracts for presentation at the November American Public Health Association Convention in San Diego: Musham, C. and Graber, D., "The Role of Medical Professionals in Environmental Health Risk Communication;" Musham, C. and Graber, D., "The Role of Public Opinion Research in Environmental Health Risk Communication Program Development: A Model;" and Musham, C. and Graber, D., "The Impact of Physician Characteristics on Environmental Health Risk Patient Education."

    - Abstracts (46)

31. Dr. Catherine Musham participated in a one-day seminar on risk communication sponsored by Clemson University. As a result of this

conference, the Outreach program initiated a project assessing undergraduate and graduate education relevant to risk communication activities and responsibilities.

32. Continued coordination efforts with Dr. John Eureta of the University of South Carolina in establishing a South Carolina Risk Perception and Communication computer network.

33. Collected and organized research literature relevant to risk perception and communication. A catalog of this literature is now available to all Outreach Division researchers as well as other EHAP personnel. The major categories of published research include: Environmental Risk Perception, Environmental Equity, Industry-based Risk Communication Efforts, Community-initiated Environmental Health Programs, and Medical Practitioners and Environmental Health. This catalog will be continually updated.

34. Completed revisions of dental educator survey. The study was designed to assess dental educators' perceptions regarding the need for environmental health education in graduate school. Will submit to various journals for publication in the first quarter of year four.

35. Conducted an attitude and opinion study of South Carolina Lowcountry residents who catch and consume mercury-contaminated fish. The purpose of this study is to measure the awareness, knowledge and attitudes of this target population as a first step in developing a public risk communication program on the dangers of mercury poisoning.

    - Survey instruments (written and oral) (47)

36. Collaborated with Dr. Janet Z. Temple of MUSC's Department of Environmental Health Sciences on a survey of environmental management practices in public schools.

    - Sample population listing (48)

    - Survey instrument (49)

37. Completed the preliminary planning phase for testing the feasibility of using the Crossroads "Purity" Round table videotapes as educational tools.

    - Phase one documentation (50)

38. Received an agreement to participate in stakeholder study from Dupont and Allied chemical. Refined survey instrument and have completed first phase of data collection (interviews of Allied middle managers).

39. Resubmitted the manuscript "Environmental Health Training in Family Practice Residency: A Survey of Program Directors." to the editor of Family Medicine. The manuscript has been accepted for publication.

    - Letter of acceptance (51)

40. Catherine Musham, Ph. D. presented the results of the paper "Environmental Preparedness: Helping Communities Plan for Environmental Incidents" at the American Nuclear Society's Fifth Topical meeting on Emergency Preparedness and Response in April.

    - Manuscript (52)

41. Submitted two abstracts to the Annual Association of Public Health convention in San Diego in November 1995. Both were accepted as paper presentations.

    - Copies of abstracts (53)

42. Submitted two abstracts for the annual Society of Risk Analysis Conference in December 1995.

    - Copies of abstracts (54)

43. Started initial planning of Medical Education Reform research group with Dr. David Graber , Department of Health Services Administration, and Dr. Jan Bellack, Associate Provost for Educational Programs.

44. Prepared the manuscript "Patients' Perceptions of Physicians as Environmental Health Information Sources." Co-authors were Catherine Musham, Ph.D., David Graber, Ph.D., and Mark T. Godenick, M.D., M.P.H.

    - Copy of manuscript (55)

Milestones and Products Projected for Year 4

1. Will conduct a study in conjunction with the Department of Environmental Health Sciences examining the perceptions of environmental engineering educators at undergraduate schools.

2. The Medical Education Reform Research group (with Drs. Graber and Bellack) will conduct surveys on three medical educator groups or perceived need for inclusion of environmental health and other non-traditional topics into curriculum.

3. Will submit the first dental survey for publication.

4. Will complete the focus groups for the childhood lead poisoning study and develop more community-sensitive communication tools to be used by the Childhood Lead Poisoning Group in Charleston.

5. Will present the aforementioned research report manuscripts at the American Public Health Association Convention and the Society for Risk Analysis Annual Conference.

    - Copies of manuscripts

6. Will implement an educational program in elementary and high school classes using the Crossroads Series tapes as educational tools.

7. Will continue involvement in "Blackville Speaks Out" including evaluation efforts (telephone survey and focus groups to be conducted at midterm and at the end of the program).

8. Will continue participation in the "Stakeholders Perceptions Study" with Dr. Abe Wandersman by conducting several focus groups of community residents. This study will be complete and ready for publication by Spring 1996.

9. Will include "Development of Risk Perception" component in "Risk Communication" training program developed by Dr. Jan Temple.

10. Will continue involvement with Enterprise Community activities.

11. Will complete analysis of survey results on mercury contamination in fish. Will complete article for MUSC newspaper.

    - Copy of article

4.1.3 Publications/Information	
Program Information Coordinator:	Richard Jablonski
Public Information Specialist (Publications):	Cathi Bare
Public Information Specialist:	Amy Hovatter
Public Information Specialist (Database):	Jill Tompkins

Milestones and Products for Year 3

1. Developed and implemented MUSC/EHAP "home page" on the World Wide Web, a graphical interface to the world's largest computer network. To access: http://www.ehap.musc.edu

2. Published and mailed July-August EHAP News & Information

   - EHAP News & Information (56)

3. Inaugurated design process for new generation of MUSC/EHAP brochures and information sheets. Published July EHAP Fact Sheet.

   - EHAP Fact Sheet (57)

4. Published student recruitment posters for MUSC's master's program in Environmental Studies and Ph.D. program in Environmental Risk Assessment. (7-9/94).

   - Master's recruitment poster (58)

5. Continued tracking television air dates of MUSC/EHAP Socratic dialogues on environmental risk, *In Search of Purity* and *Purity Revisited.* (7-9/94)

   - Updated report and air list (59)

6. Revisited earlier efforts to develop publication-exchange relationship with environmental organizations nationwide. Contacted organizations and are adding interested groups to Crossroads database and are exchanging newsletters and publications.

7. Designed and published January 1995 newsletter.

   - EHAP News & Information (60)

8. Provided publication and logistical support for first meeting of EHAP External Advisory Group, November 20-22, 1994, in Charleston.

- Dr. Jones' overview (61)
- Dr. Fleming's and Dr. Musham's outreach materials (62)
- Master's program presentation (63)
- External Advisory Group charge/overview book (64)

9. Continued design process for a new generation of MUSC/EHAP brochures and information sheets.
   - EHAP Accomplishments (65)
10. Designed publications and provided logistical support for Blackville community intervention project.
11. Published and mailed spring newsletter.
    - EHAP News & Information (66)
12. Published/distributed announcement of Dr. Lawrence Mohr's appointment as director of MUSC/EHAP (5/95).
13. Published/distributed EHAP Fact Sheets on development of an MUSC/EHAP "home page" on the World Wide Web.
    - Fact sheets (67)
14. Began planning and production of MUSC/EHAP video series, which ultimately will include several short videotape programs on various MUSC/EHAP activities. First program will focus on outreach activities in Blackville, SC (4-6/95).
15. Planned publication and logistical support for second meeting of EHAP External Advisory Group, scheduled July 24-25, 1995, in Charleston.
16. Attended Kickoff Meeting for International Risk Assessment/Risk Management Forum Steering Committee, May 3, 1995, in Washington, DC.
17. Provided publication and logistical support for first meeting of International Risk Assessment/Risk Management Forum Steering Committee, June 15-16, 1995, in Charleston, SC.

18. Planned publication and logistical support for second meeting of International Risk Assessment/Risk Management Forum Steering Committee, scheduled July 25-26, 1995, in Charleston, SC.

19. Submitted news releases to MUSC's weekly newspaper, *The Catalyst*.. Four stories were published.

    - Copies of stories (68)

20. Continued in-house newspaper, magazine and publication "clip file."

Milestones and Products Projected for Year 4

1. Will continue development and implementation of MUSC/EHAP "home page" on the World Wide Web.

2. Will continue publication of *EHAP News & Information* newsletter. Next anticipated publication date is 8/95.

3. Will plan and produce of MUSC/EHAP video series, which ultimately will include several short videotape programs on various MUSC/EHAP activities. First program will focus on outreach activities in Blackville, SC. Anticipated completion date of first program: Year 4, Quarter 2.

4. Will design and publish new generation of MUSC/EHAP brochures and information sheets.

5. Will provide publication and logistical support for meetings of EHAP External Advisory Group. Next meeting is 7/24-25/95.

6. Will provide publication and logistical support for meetings and programs relating to the ongoing International Risk Assessment/Risk Management Forum. Next Steering Committee meeting: 7/25-26/95. Meetings scheduled in the United Kingdom (9/95), Washington, DC (11/95) and Charleston, SC (3/96).

7. Will continue in-house newspaper and publication "clip file."

4.2	Department of Environmental Health Sciences (DEHS) - Education and Training Initiative
Project Director:	Janet Z. Temple, Ph.D.
Faculty:	William Hotle
Faculty:	Marc Hunt, CIH
Faculty:	Andy Rowland
Administrative Specialist:	Gerri Hollis
Accounting Technician:	Lisa Burkhardt

Executive Summary

The primary objective of this project 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 that the current and future work force has the skills, knowledge and abilities to carry out its mission today and in the future. It is also a priority 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 in environmental cleanup and government, business, and industry restoration issues.

The Department of Environmental Health Sciences (DEHS) is involved in the Education and Training Initiative. An Advisory Committee has been established to render guidance for this task. This committee includes representatives from EPA, OSHA, DOE, DOD, unions, educators, public interest groups and the health care community. The fifth meeting of the Advisory Committee is scheduled for May in Charleston, SC.

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 may be modified for application to other professions.

Two Professional Development seminars have been designed and developed during Year 3. The programs vary in length, and include: 1) "Risk Communication"-an introduction to risk communication methods and theory; and, 2) "Executive Overview of Risk Analysis"-a short course to provide basic information in risk assessment, risk management and risk communication for senior managers.

In November, the first course, "Risk Communication" was pilot tested to the Advisory Committee and received beneficial comments from committee members. A second pilot was conducted in March with a final review held during May's Advisory Committee meeting. The second course, "Executive Overview of Risk Analysis," was also presented at May's meeting.

During Year 4 DEHS proposes to do the following: 1) Continue to utilize the Risk Management Advisory Committee; 2) Add a chapter to the Risk Communication course entitled, "Utilization of Risk Perception Research;" 3) Conduct demonstrations of the professional enhancement series; 4) Complete Executive Overview of Risk; 5) Support the Enterprise Community initiative; 6) Continue research focusing on risk education, training and management practices; 7) Identify and develop mechanism(s) to include Risk education/training into the S. C. Statewide Systemic Initiative for math and science; and, 8) Disseminate training and research results.

Objectives

1. To address worker and management needs in a rapidly changing environment.

2. To ensure that resources are available to assure the current and future work force has the skills, knowledge, and abilities to carry forth its mission today and in the future.

3. To ensure that all groups within our society participate in the successful cleanup activities of environmentally hazardous sites.

Milestones and Products for Year 3

1. Examined training needs of government and industry facilities.

2. Through maintaining our off-site library, we developed an index of reference material.

    - Index of reference material (69)

3. Developed a revised needs assessment instrument to better ascertain the level of risk awareness of the subject groups. It will be distributed to various groups upon request and can be further customized to meet their needs.

4. Pilot-tested the second of the seminar series, "Decision Making in Environmental Risk Management," during the August meeting of the Advisory Committee. This course is an introduction to how risk concepts and theory impacts management decisions in regards to health and the environment.

5. The Advisory Committee convened November 30 - December 1, 1994, where the third of the seminar series, "Risk Communication" was

pilot-tested. This course is an introduction to the importance and methods used in risk communication of environmental hazards.

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

7. Continued course development for the second Professional Development Seminar entitled, "Decision Making in Environmental Risk Management." This course is an introduction to how risk concepts and theory impacts management decisions regarding health and the environment.

8. Conducted customized risk training for the Savannah River Site's Citizen Advisory Board on October 1-2 as an introduction to risk management.

9. Pilot-tested "Risk Communication," the third of the seminar series, in March.

10. Completed course development for the first Professional Development Seminar entitled, "Concepts of Risk Analysis." This course is an introduction to the concept of risk, the risk assessment process (specifically for hazardous waste site remediation), risk management and risk communication. The course was pilot tested to the Advisory Committee February 1- 2 in Charleston. Members of EHAP, MUSC, the Department of Energy and the Savannah River Site attended this seminar.

11. Continued course development for the third Professional Development Seminar entitled, "Risk Communication"-an introduction to risk communication concepts and practice. The second pilot of this course was conducted in March.

12. Presented guest lectures on risk communication and risk assessment to a special topics marine biomedical and environmental sciences class at the Grice Marine Lab on March 24.

13. Continued to consider an industry partnership.

14. Began to discuss feasibility of an Idaho National Engineering Laboratory (INEL) Risk Training program.

15. Initiated a discussion with Governor Beasley's office to incorporate Risk Education and Training into math and science reforms for South Carolina.

16. The Risk Management Advisory Committee convened on June 1-2. The fourth of the seminar series, "Executive Overview of Risk Analysis" was pilot-tested during the meeting. Executives are faced with complex challenges as they assume responsibility and liability to manage and communicate public, occupational, and environmental health risks associated with exposures to toxic substances to diverse stockholders. This program is designed to increase awareness and understanding of the risk analysis process and recognize commitment and support necessary to implement a responsible and responsive corporate policy.

    - List of committee members (70)

    - Copy of meeting agenda (71)

17. Continued course development for the second Professional Development Seminar, "D· ·sion Making in Environmental Risk Management," which now .s final approval. This course is an introduction to how risk concepts and theory impacts management decisions in regards to health and the environment.

    - Copy of agenda, course manual, slides/overheads and course evaluation (72)

18. Continued course development for the third Professional Development Seminar, "Risk Communication," an introduction to risk communication concepts and practices. The second pilot of the Risk Communication course was conducted in March and the final Risk Management Advisory Committee review and editing in June.

    - Copy of agenda, course manual, slides/overheads and course evaluation (73)

19. Continued course development for the fourth Professional Development Seminar, "Executive Overview of Risk Analysis." Final revisions are underway with a second pilot to be delivered.

    - Copy of agenda, course manual, slides/overheads and course evaluation (74)

20. With assistance from Dr. Catherine Musham and Mr. Dylan Holmes of EHAP, we disseminated a "Survey of Environmental Risk

Management Practices in Schools" to ascertain Environmental Risk Management practices in public schools. The instrument was distributed to state administrators responsible for planning, budgeting, building, and renovations of school facilities. Preliminary findings will be disseminated at their 1995 summer conferences. It is anticipated that a need may exist for a clearinghouse for environmental health and risks management practices for public schools nationwide.

21. Submitted abstract to Society for Risk Analysis.

    - Copy of abstract (75)

22. Developed proposal for an environmental health topic in undergraduate engineering schools study with Dr. Musham of EHAP.

23. Conducted "Risk Communication" pre-conference workshop on June 9 for the National Association of Environmental Professionals in conjunction with Dr. Max Lum formerly with ATSDR and now with NIOSH.

24. Presented "Lead Health Risks" at premier presentation of Charleston Childhood Lead Poisoning Prevention video.

25. Addressed the Charleston County Health Department as a guest speaker regarding the future of Environmental Health.

26. Responded to request from Westinghouse Savannah River Company (WSRC) and their Citizen's Advisory Board for assistance in addressing environmental human health effects. Scientists and engineers from WSRC could not satisfactorily address such concerns. Recommendations included briefing an occupational physician and pediatrician from Georgia and South Carolina when health issues surfaced.

Milestones and Products Projected for Year 4

1. Will continue to utilize the Risk Management Advisory Committee to render guidance and support to this initiative.

2. Will design and develop an educational module entitled, "Utilization of Risk Perception Research" for inclusion in the Risk Communication course.

3. Will conduct three demonstrations of course(s) in the Professional Enhancement Series.

4. Will finalize the Executive Overview of Risk Analysis course.

5. Will support the Enterprise Community initiative through leadership, establishing partnerships, community education and training, research, and other public outreach as assigned.

6. Will conduct research focused on risk training/education and management.

7. Will create a partnership with S.C. Statewide Systemic Initiative for math and science to infuse risk education/training or identify and develop mechanism(s) to include risk education/training into the S. C. Statewide Systemic Initiative for math and science.

8. Will disseminate findings through publications and presentations.

5.0 SCIENCE PROGRAMS

5.1 Biomedical Research Projects

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

Executive Summary

Beryllium is used in nuclear and lighting industries. It is responsible for a chronic respiratory disease progressing to respiratory insufficiency in a percentage of individuals exposed to it by inhalation. The possible health effects of beryllium are of emerging concern, particularly under circumstances where exposure may be intermittently or continually high.

Two apparently distinct patterns of pulmonary disease may be observed. Acute pneumonitis and chronic interstitial beryllium disease represent a hypersensitivity reaction. The mechanisms responsible for chronic beryllium disease (CBD) are far from being understood. Nevertheless, it is important to stress that the lung pathologies of CBD and sarcoidosis are identical. Both are characterized by the existence of a chronic lung granuloma. This means that if this research can deduce the relationship between CBD and beryllium, we stand a very good chance of discovering the environmental trigger for sarcoidosis and other diseases.

We made some progress 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 cells. However, in the chronic form, patterns found by studying the minute structure of tissue suggest that beryllium can elicit a specific immune response, compartmentalized into the lung.

As CBD appears to be an auto immune response where beryllium plays the role of an antigen or foreign matter, the most likely sequence of events is as follows: inhaled beryllium enters normal alveolar cells that can retain beryllium for months or years. In these cells, beryllium may affect the binding of peptide(s) to certain other protein (HLA-class-II) molecules. In mice, only those possessing a specific phenotype develop a similar disease. 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.

Our hypothesis is that a particular beryllium ion binds through its positive charges to a set of 2 or 3 negatively charged residues in the MHC chain. This, in turn, will interfere with the binding of normal peptides to this MHC molecule (DP). It is therefore of critical importance to determine the structure of the MHC-associated peptides and to study the effect of beryllium on their binding.

Notes on Terms

Major histocompatibility complex proteins, usually abbreviated as MHC, are molecules known to play a critical role in the development of antibodies in that they bring a "foreign" peptide to which the antibody is to be attached to the surface of the macrophage, where the T-cell can bind to it.

A haplotype is the genetic constitution contributed by either parent.

T-cells recognize the way in which peptides bind the MHC molecules. When they achieve this recognition, T-cells secrete lymphokines or chemical signals that activate other components of the immune system.

If beryllium modifies the way certain peptides bind to MHC proteins, the activity of the immune system could be altered, leading to either inappropriate or diminished activity.

Objectives

1. To determine the immunological mechanisms responsible for the environmental hazard created by beryllium.

2. To isolate the MHC-bound peptides from rats and humans that are associated with susceptibility and resistance to beryllium disease and to compare their structure.

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

Milestones and Products for Year 3

1. Completed the production of monoclonal in August 1994, and verified by ELISA the production (in 1% fetal calf serum) of the FPLC purified monoclonal. The FPLC is fully operational and performs excellently.

2. Modified a recycling-coupling affinity chromatography program that allowed us to bind these monoclonals to N-hydroxy succinimide-activated sepharose. This program resulted in binding as much as 16

mg of protein-A purified specific monoclonal antibodies to each column.

3. Completed the isolation of the I-A^k and the I-E^k protein molecules from the membrane of CH1 cells.

4. Produced a human monoclonal antibody against class-II HLA(L-243).

5. Extracted a membrane from a human cell line homozygous for HLA-DR4. We used the protocol previously used for the mice cell line. The product was used to perform gel migration in polyacrylamide followed by transfer of the protein on a nitrocellulose membrane subsequently incubated with the monoclonal antibody purified from clone L-243, a technique known as a Western blot. It clearly showed a single band migrating at the expected molecular weight (64kD), confirming that we had extracted class-II molecules from the human cell line.

6. Produced a large number ($1x10^{10}$; 10 liters) of the cell line homozygous for HLA-DR4. At that time we will prepare the affinity columns and complete class-II purification and peptide extraction. Structural studies of the above peptides were performed in the laboratory of Dr. Daniel Knapp and involved first reverse phase-HPLC followed by tandem mass spectrometry of the dominant peptides (present at concentrations >80pmol).

7. Dr. Goust attended a conference on Beryllium Related Diseases held at the National Institute of Environmental Health Sciences at Research Triangle Park November 8-10, 1994. This event was co-sponsored by NIOSH, OSHA and the DOE.

8. The animal models of CBD were found to barely approximate the human disease, prompting us to abandon this line of work. In regard to human CBD, epidemiological data concerning the predictive value of the HLA-DP previously reported to be found in 98 percent of CBD cases, showed that it was much less predictive than initially claimed, and that other class-II molecules, namely HLA-DR also contributed.

9. The most important development followed our meeting with Dr. L. Newman and his team. We decided to collaborate with him to determine the effect of beryllium on peptide presentation.

After the second quarter, DOE grant funding for this project was discontinued. This decision was made so that EHAP's biomedical research could focus on trichloroethylene (TCE) studies.

The Immunological Mechanisms Associated with Beryllium project is pursuing funding from other sources.

5.1.2 Assessment of Genetic Risks to Environmental Diseases

Project Director:	Janardan P. Pandey, Ph.D.
Co-Investigator:	Gillian M.P. Galbraith, M.D.
Laboratory Technician:	P. Werner

Executive Summary

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.

The broad spectrum of environmental diseases includes those known to result from occupational or other exposure to defined environmental toxins, and those in which the role of the environmental insult is less clear. Berylliosis is an example of the first group which offers a model for study of disease susceptibility throughout the spectrum of environmental diseases. Exposure to beryllium, usually by inhalation of particulate beryllium, results in chronic, progressive, destructive lung disease in some, but not all, individuals exposed. This in itself suggests that factors exist which determine disease susceptibility. Current evidence indicates that the disease process is mediated, at least in part, by the individual's immune response to beryllium, and it is therefore reasonable to suspect that genes controlling this immune response may be involved in determination of disease susceptibility. This hypothesis is supported by data which indicate that susceptibility is associated with the possession of a particular cell surface molecule, which is produced by a gene called HLA-DPB1*0201, and which is involved in the initiation of the immune response.

Our studies to date have shown that other substances produced in the immune response may be involved in susceptibility to the disease. For example, a substance called TNF-a, which is produced by immune cells, is suspected to be responsible for many of the pathological changes in this disease. We have shown that exposure of certain immune cells to beryllium in the laboratory results in the "switching on" of the gene which produces TNF-a. This is particularly interesting since the amount of TNF-a which is produced by an individual in response to a given stimulus appears to depend on allelic variations in the TNF-a gene. This is one hypothesis that will be examined in the studies described in this report. Most recently, we have shown that human macrophages stimulated by immune complexes switch on the TNF gene (product listed below). Also, we have recently investigated

the role of HLA antigens and Ig allotypes in IgA nephropathy (product listed below).

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

Objective 2

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

Strategy 2

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

It should be noted that human material for these studies has already been obtained from several sources and certain of these sample sets have been characterized with respect to one or more of the genetic markers listed above.

In such cases, it is therefore unnecessary to duplicate the findings of our collaborators.

Notes on Terms

A lipopolysaccharide is a molecule or compound in which lipids and polysaccharides are linked, as in cell membranes.

Milestones and Products for Year 3

1. Characterized TNF and IL-1 markers in serum DNA.

    - Manuscript by Galbraith, G.M.P. and Pandey, J.P. Tumor necrosis factor alpha (TNF-α) polymorphism in alopecia areata. Submitted for publication in the *Journal of Experimental Medicine* . (76)

2. Examined the expression of TNFα and IL-1β in activated monocytic cells, by northern and slot blot hybridization studies.

    - Manuscript by Galbraith, G.M.P., Pandey, J.P., Schmidt, M.G., Arnaud, P., and Goust, J.M. TNF-α gene expression in human monocytic THP-1 cells exposed to beryllium. Submitted for publication in the *Archives of Environmental Health* . (77)

3. Allotyped silicosis patients. Performed a statistical analysis of Ig allotypes and silicosis data.

4. Performed preliminary studies of Ig allotypes on a limited number of serum samples from patients with berylliosis.

5. Developed new methodology (ELISA) for determination of Ig allotypes. The advantages of this method include increased reliability, and the potential for automation and quantitation of data. We have developed assays for three allotypes to date, and have tested them on a number of sera of known allotypes.

6. Completed a statistical analysis of available allotype data in berylliosis.

7. Completed an analysis of Gm and Km allotype data in antibody responses to *Moraxella catarrhalis.*

    - Manuscript by Goldblatt, D., Scadding, G.K., Lund, V.J., Wade, A.M., Turner, M.W., and Pandey, J.P. Association of Gm Allotypes with the Antibody Response to the Outer Membrane Proteins of a Common Upper Respiratory Tract Organism,

Moraxella catarrhalis. *Journal of Immunology* 1994; 153:5316-5320. (78)

8. Examined TNF-a gene expression in normal human monocytic cells exposed to stimuli including beryllium, immune complexes, and lipopolysaccharide.

9. Completed investigation of TNF-a gene expression in activated human macrophages.

    - Manuscript by Virella, G., Munoz, J.F., Galbraith, G.M.P., Gissinger, C., Chassereau, C., Lopes-Virella, M.F., "Activation of Human Monocyte-derived Macrophages by Immune Complexes Containing Low Density Lipoprotein." *Clin Immunol Immunopathol,* 1995, in press. (79)

10. Studied role of HLA, Gm, and Km genes in IgA nephropathy.

    - Manuscript by Luger, A.M., Komathireddy, G., Walker, R.E.W., Pandey, J.P., Hoffman, R.W. , "Molecular and Serologic Analysis of HLA Genes and Immunoglobulin Allotypes in IgA Nephropathy." *Autoimmunity* 1994; 19:1-5 (80)

11. Continued investigation of racial differences in cytokine polymorphisms. Analyzed data from this investigation.

Milestones and Products Projected for Year 4

DOE grant funding for this project has been discontinued. This decision was made so that EHAP's biomedical research can continue to focus on trichloroethylene (TCE) studies. Much of the progress from the above project will be applied to the "Immunogenetic Epidemiology of Scleroderma" project, which is led by Dr. Pandey.

The Assessment of Genetic Risk to Environmental Diseases project is pursuing funding from other sources.

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.

Executive Summary

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

We have worked to characterize a rabbit polyclonal antibody that was raised against trichloroethylene-protein adducts. As detailed previously, this work is concerned with establishing the specificity and sensitivity of the antibody, which will provide information that will be of critical importance when we begin to develop an immunoassay for TCE adduct detection in human blood samples.

We are continuing work to synthesize compounds for use to characterize the specificity of the antibody (i.e., what does the antibody recognize, and how much cross-reactivity exists). Previous methods utilized to synthesize a dichloroacetylated lysine derivative were not successful, and one of the major efforts during this quarter has been to use alternative synthetic routes to make the inhibitor product. We have been successful at synthesizing the less reactive thiolacetate derivative of dichloroacetyl chloride, ethyl dichlorothiolacetate. This reagent was purified by fractional distillation, and analyzed by GC-MS and proton NMR spectroscopy. This reagent was then used to make the first antibody inhibitor. Briefly, an excess of dichlorothiolacetate was reacted with L-lysine, and the product precipitated from solution upon cooling to 4°C. The dichloroacetylated lysine product was then washed in hot ethanol, and subjected to analysis by HPLC, MS, and NMR spectroscopy. The product was found to be >99% pure, and its structure was confirmed by two-dimensional NMR, which was performed in collaboration with Dr. John Oatis in MUSC's Department of Pharmacology.

The dichloroacetyl lysine inhibitor was then sent to Dr. Neil Pumford who utilized the inhibitor in competitive ELISA (enzyme-linked immunosorbent assay). This inhibitor was found to displace the antibody (effective inhibitor concentration producing 50% inhibition was approximately 50 μM), and was about 10,000-fold more effective than acetyl lysine (i.e., no chlorine atoms on the molecule).

We are now working to synthesize the remaining two inhibitors (mono- and trichloroacetyl-lysine), which should give us the means to determine what type of chemical adducts the antibody will recognize. The most efficient inhibitor, which we expect will be the dichloroacetyl lysine, will then be used to establish antibody sensitivity.

Objectives

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

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

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

Milestones and Products for Year 3

1. Completed modification of human serum albumin with dichloroacetic anhydride.

2. Began immunoaffinity chromatography purification of modified human serum albumin with Dr. Neil Pumford of the University of Arkansas.

3. Developed a working immunoaffinity chromatography column that will separate adducted from non-adducted proteins.

4. Found that plasma proteins from TCE-treated rats were shown to contain TCE-protein adducts, but only after immunoaffinity purification.

3. Found TCE adducts in the lungs of TCE-treated mice.

4. Began dichlorothiolacetate synthesis. Preliminary NMR data are consistent with the structure, and indicate a purity of about 95 percent.

5. Synthesized dichloroacetyl lysine and confirmed its structure and purity.

6. Utilized this inhibitor in competitive ELISA and shown that it effectively displaced antibody binding.

7. Synthesized the mono- and trichlorothiol-acetates for use in preparing the remaining inhibitors in the series.

8. Dr. David McMillan submitted an abstract on the above work that will be presented at the International Congress of Toxicology VII in July in Seattle, WA. The abstract will be presented in a poster-discussion session topic entitled, "Covalent Binding."

Milestones and Products Projected for Year 4

1. Will develop a high performance liquid chromatographic (HPLC) separation of amino acids to isolate and purify TCE-amino acid adducts.

2. Will perform chemical modification of a model peptide with dichlorothiolacetate, digest the modified peptide with the proteolytic enzyme pronase, and purify the amino acids by HPLC; will optimize procedure as necessary.

3. Will derive amino acids for GC-MS analysis and will analyze modified peptide by tandem mass spectrometry in Dr. Daniel Knapp's laboratory.

4. Will purify TCE-adducted proteins from TCE-exposed mice by immunoaffinity chromatography; perform pronase digestion and HPLC analysis as described above. Will prepare a manuscript on the purification of the TCE adducts.

    - Copy of manuscript

    Will prepare a mono- and trichloroacetylated immunogens by chemical modification of keyhole limpet hemocyanin; will immunize rabbits, collect and characterize antisera. Will complete manuscript on the preparation of these immunogens.

    - Copy of manuscript

6. Will determine the effect of various drug metabolizing enzyme inhibitors on the extent of covalent binding of TCE to protein in mice and will complete a manuscript on this analysis.

    - Copy of manuscript

7. Dr. David McMillan will present "Covalent Binding" at the International Congress of Toxicology VII in July in Seattle, WA. This abstract is about synthesizing the mono- and trichlorothiol-acetates for use in preparing the remaining inhibitors in the series.

5.1.4 Species Comparison of Trichloroethylene-Induced Peroxisome Proliferation and Induction of DNA Syntheses	
Project Director:	JoEllyn M. McMillan, Ph.D.
Technical Support:	Stacey Allen, B.S.

Executive Summary

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

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

TCE falls into a category of compounds known as peroxisome proliferators, for example, they induce an increase in the number of peroxisomes in a cell. Peroxisome proliferators also induce a characteristic pattern of biochemical responses in the liver. Hepatocarcinogenesis is a common property of all peroxisome proliferators tested thus far; however, this response is not usually associated with direct DNA damage by the compound. Increased production of hydrogen peroxide, which may cause indirect DNA damage, and the propensity of these compounds to induce hepatocyte replication have been argued to contribute to their ability to cause hepatic cancer in certain laboratory animal species.

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

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

Objectives

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

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

Milestones and Products for Year 3

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

    - Experimental protocols for TCA treatment of rat and mouse hepatocyte cultures and human hepatoma cell lines (81)

2. Optimized hepatocyte culture conditions for studies on TCE metabolite-induced peroxisome proliferation and induction of DNA synthesis: (a) dose-response relationship.

    - Preliminary data on the dose-response relationship for TCA-induced peroxisome proliferation in rat and mouse hepatocytes and human hepatoma cell lines (82)

    - Preliminary data on the dose-response relationship for TCA induction of DNA synthesis in rat and mouse hepatocytes and human hepatoma cell lines (83)

3. Optimized hepatocyte culture conditions for studies on TCA-induced peroxisome proliferation and induction of DNA synthesis: (a) dose-response relationship.

4. Compared the ability of TCA to induce peroxisome proliferation with that of clofibrate, a compound known to induce peroxisome proliferation.

5. Compared the induction of DNA synthesis for TCA with that of epidermal growth factor, a compound known to induce cell replication (i.e., DNA synthesis).

6. Continued to optimize hepatocyte culture conditions for studies on TCA-induced peroxisome proliferation and induction of DNA synthesis with reference to the dose-response relationship.

   - Data on TCA-induced peroxisome proliferation in mouse hepatocytes (84)

   - Data on TCA induction of DNA synthesis in rat hepatocytes and human hepatoma cell lines (85)

7. Continued to compare the ability of TCA to induce peroxisome proliferation with that of clofibrate, a compound known to induce peroxisome proliferation.

8. Continued to compare the induction of DNA synthesis for TCA with that of epidermal growth factor, a compound known to induce cell replication (i.e., DNA synthesis).

9. Wrote abstract: J. M. McMillan, D.T. Kurtz, and D. J. Jollow, "Trichloroacetic Acid Induction of Peroxisome Proliferation in Mouse and Rat Hepatocytes and a Human Hepatoma Cell Line." Abstract will be presented at the VII International Congress of Toxicology Meeting in Seattle, Washington from July 2-6.

   - Copy of abstract (86)

10. In continuation from earlier work, optimized hepatocyte culture conditions for studies on TCA-induced peroxisome proliferation and induction of DNA synthesis: (a) dose-response relationship.

    - Data on TCA-induced peroxisome proliferation in rat and mouse hepatocytes and human hepatoma cell lines (87)

    - Data on TCA induction of DNA synthesis in rat hepatocytes and Hep3B cells (88)

11. Optimized conditions for immunoblots of the peroxisomal bifunctional enzyme. Produced a Western blot protocol using antibody to the rat peroxisomal bifunctional enzyme obtained from Dr. Michael Kelly, Rhone Poulenc-Rorer Pharmaceuticals. (Protocol 1)

    - Copy of Western blot protocol (89)

12. In continuation from earlier research, compared the ability of TCA to induce peroxisome proliferation with that of clofibrate, a compound

known to induce peroxisome proliferation in both mouse and rat hepatocytes.

13. Also in continuation from earlier research, compared the induction of DNA synthesis for TCA with that of epidermal growth factor, a compound known to induce hepatocyte cell replication (*i.e.* DNA synthesis).

14. Obtained outside contact for learning human hepatocyte isolation. This will provide expertise for future studies to examine this phenomenon in human hepatocytes. Arrangements were made with Dr. Steven D'Ambrosio, Ohio State University, to observe isolation of human hepatocytes.

    - Copy of letter outling arrangements (90)

Milestones and Products Projected for Year 4

1. Identify protein markers for molecular quantitation (*i.e.* immunoquantitation &/or mRNA quantitation) as indices of peroxisome proliferation.

2. Continue studies on TCA- and DCA- induced peroxisome proliferation (using both enzymatic and molecular markers) and enhancement of DNA synthesis in rat and mouse hepatocyte cultures and in the HepG2 and Hep 3B human hepatoma cell lines.

    - Copies of data

3. Compare the ability of TCA and DCA to induce peroxisome proliferation (using both enzymatic and molecular markers) with that of clofibrate and other known peroxisome proliferators. Produce data on the dose-response relationship for TCA-induced peroxisome proliferation (enzymatic markers) in rat and mouse hepatocytes and human hepatoma cell lines.

    - Copies of data

4. Compare the induction of DNA synthesis for TCA and DCA with that of epidermal growth factor, a known mitogen. Will produce comparative data for clofibrate (peroxisome proliferation) and epidermal growth factor (DNA synthesis) in rat and mouse hepatocytes and human hepatoma cell lines.

    - Copies of data

5. Attend International Congress of Toxicology VII Meeting (July 2-5, 1995) to present results on TCA induction of peroxisomal enzymes in rat and mouse hepatocyte cultures and human hepatoma cell lines.

5.1.5 Disease Initiation by Environmental Toxins

Project Director: Thomas A. Dix, Ph.D.

Executive Summary

A central role for O_2-derived oxidants in human disease initiation and propagation has been demonstrated. These species are generated as part of human metabolism; consequently, a multicomponent antioxidant system has evolved to keep the reactivity of these species under control in normal tissue. However, various agents that directly or indirectly generate oxidants have the potential for disease initiation by increasing these species to levels that overwhelm the defenses.

A potentially important, although under-evaluated, source of oxidant generating agents is the environment. In tests conducted outside of the organism (*in vitro*), a number of chemicals found in the environment either generate oxidants directly under biomimetic conditions, or interact with O_2-metabolizing enzymes to effect oxidant release. The role of environmental agents within the organism (*in vivo*) is less clear, however, as it is difficult to establish a cause and effect relationship between chemical exposure, oxidant generation, and disease initiation. A long-term goal of our research program is to establish this relationship, which would support further control of release of toxic agents into the environment.

This goal can be approached using the following strategy. Over the last few years, we have developed methods to generate each of the physiologically significant O_2-derived oxidants specifically and have evaluated the mechanisms by which these species react with biomolecules (in particular, lipids and nucleic acids). Oxidants of interest include super oxide (O_2^-), the hydroxyl (HO·), peroxyl (ROO·), alkoxyl (RO·), and perhydroxyl (HOO·) radicals, hydrogen peroxide (H_2O_2), and hypochlorous acid (HOCl). We have established that the oxidants that react with lipids are HOO·, HO·, and ROO·, and that each reacts by a different mechanism.

Potentially, the isolation of lipid-derived products of oxidant attack would serve as a marker for generation of specific oxidants (and might imply a site and mechanism of generation); however, lipid-derived fatty acid metabolites are degraded extensively before excretion in the urine. This is not the case with oxidized nucleic acid material. Ames and colleagues have demonstrated that very small amounts of oxidized DNA bases can be noninvasively

collected from the urine and analyzed; the levels of material collected correlate to the existence of tissue pro-oxidant states, although a direct link to specific oxidant generation has not been done. Preliminary results from our laboratory have established that HOO·, HO·, and ROO· react with DNA by different mechanisms, which implies that the base-derived products of each oxidant's attack can be developed as biomarkers for the formation and reaction of the individual oxidants *in vivo*.

Objective

To establish a cause and effect relationship between chemical exposure, oxidant generation, and disease initiation, which would support further control of release of toxic agents into the environment.

Milestones and Products for Year 3

1. Completed product studies for the reaction of HO· with polyunsaturated lipids.

2. Completed studies to determine the mechanism by which HOO· reacts with the deoxyribose-phosphate backbone of DNA.

3. Initiated preparation of a manuscript describing the reaction of HO· with polyunsaturated lipids.

4. Completed a manuscript describing the reaction of HOO· with the deoxyribose-phosphate backbone of DNA.

5. Initiated product studies for the reaction of HO· with the DNA bases.

6. Initiated product studies for the reaction of ROO· with the DNA bases.

Milestones and Products Projected for Year 4

DOE grant funding for this project has been discontinued. This decision was made so that EHAP's biomedical research can continue to focus on trichloroethylene (TCE) studies.

The Disease Initiation by Environmental Toxins project is pursuing funding from other sources.

5.1.6 Anaerobic Dechlorination of Polychlorinated Biphenyls (PCBs) and the Biodegradation of Ether-Containing Gasoline Additives and Ether Solvents

Project Director: Harold D. May, Ph.D.
Laboratory Technician: Mary Berkaw

Executive Summary

Polychlorinated biphenyls (PCBs) have been used in a wide variety of industrial applications worldwide. Due to their stability and potential toxicity, PCBs in soils and sediments have been an environmental concern for several decades. Up until about 15 years ago, PCBs were considered to be resistant to biological degradation; however, since then, the dechlorination and biodegradation of these compounds has been documented in both the laboratory and in the environment.

However, no PCB-dechlorinating anaerobes have been isolated, and the physiology and ecology of the organisms responsible for this activity have not been determined. This makes construction of bioremediation schemes difficult. The reductive dechlorination of PCBs by anaerobes is considered an important step in the destruction of these compounds in the environment because 1) many of these environments are anaerobic; 2) more heavily chlorinated congeners are more easily attacked under anaerobic conditions; and 3) the more heavily chlorinated congeners are considered to be more toxic. Congeners are compounds closely related to another and ones that have similar effects as another.

The research of the laboratory continues to focus in two areas. The first of these is the reductive dechlorination of polychlorinated biphenyls (PCBs) under anaerobic (no oxygen) conditions. The long-term goal of this work is the destruction of PCBs *in situ* (where they exist) in anaerobic soils and sediments. The project will also deliver information on reductive dechlorination in general and on the microbial communities that are operating in these environments. The second project targets the microbial destruction (aerobic or anaerobic) of ether compounds that are used as solvents, are by-products of plastics production, or are used as octane-enhancing additives to gasoline. The latter of these compounds are methyl t-butyl ether (MTBE) and ethyl t-butyl ether (ETBE), which are commonly referred to as gasoline oxygenates.

Notes on Terms

Anaerobic dechlorination of PCBs in essence detoxifies a contaminated site. To completely dechlorinate PCBs in anaerobic environments, several dechlorinating activities will be required. This is because there are potentially

209 forms of PCBs and no one organism is capable of attacking them. Also, the number and position of the chlorines on the biphenyl rings is another element of this problem. Attack of the *ortho* positioned chlorines is rare, and hence, the characterization and development of such activity (action by organisms) could be of use in future remediation efforts.

Objectives for Anaerobic Dechlorination of PCBs

1. To enrich, isolate, and characterize the microorganisms involved in the anaerobic dechlorination of PCBs, which is needed as a first step toward understanding the microbiology of the process of bioremediation of PCBs.

2. To achieve bioremediation of soils and sediments contaminated with PCBs.

Objectives for Biodegradation of Ethers

1. To isolate and characterize microorganisms that are capable of degrading the gasoline additives MTBE and ETBE.

2. To achieve bioremediation of ground waters contaminated with the aforementioned ethers.

Milestones and Products for Year 3

Research

Project A: Anaerobic Dechlorination of Polychlorinated Biphenyls

1. The long-term goal of this project deals with the bioremediation of soils and sediments contaminated with PCBs. A better understanding of the microbiology of the process is required; therefore, enrichment, isolation, and characterization of the anaerobes involved are being pursued first. This is being done under marine, estuarine and freshwater conditions. Several marine and estuarine enrichments have been initiated under several conditions. The cultures are biologically active (gas production), and if active, then isolation and characterization of the responsible organisms will begin.

2. Began three enrichments that expressed three different types of anaerobic PCB dechlorination. One of these rapidly removes *meta* chlorines from the rings but does not attack the outer most or inner most positions, *para* and *ortho* respectively. A second enrichment line is attacking the *para* positions, however, entirely different culture conditions are required for the *para* dechlorination to be maintained.

Both of these cultures have been developed from freshwater sediments. A third culture is expressing *ortho* dechlorination in addition to *meta* and *para* dechlorinations. *Ortho* dechlorination is very rare and has only been reported twice. In both of the reported cases, the activity was very slow in development (6-12 months) and was not sustained. Our enrichment, which was developed from an estuarine sediment that was not contaminated with PCBs, showed activity in five weeks and has been sustainable.

3. We also have *meta* and *para* dechlorination ongoing in marine enrichments. The anaerobic PCB dechlorination in the marine environment has not been extensively investigated and gives us another group of potentially unique and useful organisms to examine.

4. Began to develop DNA probe technology for detecting PCB dechlorinating anaerobes in mixed populations and *in situ*. Although techniques have been published on the isolation of DNA from sediments, phenolic compounds such as humic acids that are associated with sediments interfere with analysis and must first be removed. The problem is particularly acute when extracting DNA from slurries of coal-based humic acids (25 percent dry wt/v), such as those used to maintain some of the PCB-dechlorinating cultures used in this laboratory. In collaboration with Dr. Kevin Sowers at the Center of Marine Biotechnology at the University of Maryland, a procedure for removal of high concentrations of humics has been developed. In preliminary experiments, DNA from Archaea (*Methanosarcina barkeri*), Bacteria (*Escherichia coli*) and Eukarya (*Saccharomyces cerevisiae*) added to coal-based humic acids slurries (25 percent w/v) were extracted by this technique and amplified by polymerase chain reaction (PCR). To the investigators' knowledge this is the first PCR amplification from a sample containing such a large concentration of humic acids. The technique has been refined to enable extraction and PCR amplification of DNA from as few as 10^4 whole cells in humic acids slurry. Analysis of PCB-dechlorinating enrichments will follow.

Project B: Biodegradation of Ether-Containing Gasoline Additives and Ether Solvents

5. The long-term goal of this project is the bioremediation of gasoline additives in soils and ground waters contaminated with gasoline. To accomplish this, we need to first discover organisms that can degrade these ethers and characterize their activity. Therefore, we must isolate organisms (aerobic or anaerobic) that are capable of degrading the gasoline additives methyl t-butyl ether (MTBE), ethyl t-butyl ether

(ETBE), and t-amyl methyl ether (TAME). These additives are mixed with gasoline as anti-knock and anti-smog components.

6. Four different enrichments have resulted in growth of organisms on ETBE. Macroscopic observations suggest that at least three different ether-degrading organisms are present in these enrichments. We are presently pursuing isolation of these organisms.

7. Four cultures have been isolated in pure form from enrichments growing on ETBE. One of these is known to produce t-butyl alcohol from ETBE or MTBE. Degradation analysis of the others, as well as physiological characterization, is still awaiting the completion of the laboratory renovation. Degradation of t-butyl alcohol was investigated, and as a result, an organism was isolated in the presence of t-butyl alcohol. This compound is a breakdown product of MTBE and ETBE. Degradation of the alcohol is yet to be determined.

Education

8. Presented "A Search for PCB-Dechlorinating Anaerobes" to the students in MUSC's Molecular and Cellular Biology Program on October 17. This seminar introduced the students to the biodegradation of PCBs, the anaerobic microbiology of the process, and my investigations with anaerobic PCB dechlorination.

9. Presented "Biodegradation of Cyclic Ethers and Ether- containing Gasoline Oxygenates" to MUSC's Department of Microbiology and Immunology on October 28. The presentation introduced the students and faculty to the biodegradation of cyclic ethers that are by-products of plastics production, to the biodegradation of gasoline additives that are ethers, and to my research projects in these areas.

10. Presented a three hour lecture on the biodegradation and bioremediation of hazardous wastes to advanced microbiology students in MUSC's Department of Microbiology and Immunology on December 8.

11. Presented a three-hour lecture on reductive dechlorination of halogenated organics to pollution microbiology students in MUSC's Department of Microbiology and Immunology on February 14.

12. Presented "Biodegradation of Cyclic Ethers and Ether-containing Gasoline Oxygenates" as part of EHAP's seminar series on February 23.

13. A summer undergraduate student, Aliyah Spruill, joined the laboratory for ten weeks. Aliyah is being trained in the cultivation of

environmental isolates and the use of a gas chromatograph and is assisting in the analysis of the organisms that degrade the gasoline additives (ETBE). In August she will present her results to the faculty and students involved with the summer program.

Milestones and Products Projected for Year 4

1. Will write manuscript and submit for publication the *ortho* PCB dechlorination data

   - Copy of manuscript

2. Will write manuscript and submit for publication the DNA isolation from humic acids data.

   - Copy of manuscript

3. Will submit for publication a manuscript describing the dechlorination of Aroclor 1242 by Baltimore Harbor sediments.

   - Copy of manuscript

4. Will determine the PCB dechlorinating ability of anaerobic microorganisms from Charleston Harbor sediments and compare to Baltimore Harbor sediments.

5. Will submit for publication a manuscript describing the ETBE-degrading isolates.

   - Copy of manuscript

6. Will screen Charleston Harbor for ether-degrading organisms.

7. Will continue to recruit students.

5.1.7 Biodegradation of Hydrophobic Contaminants (PCBs and Fossil Fuels)	
Project Director:	Pamela J. Morris, Ph.D.
Laboratory Technician:	Louise Weston

Executive Summary

The long term goal of this research investigation is to better understand the biodegradation of hydrophobic contaminants (e.g., fossil fuels, polychlorinated biphenyls) in soils and sediments.

The strong sorption of polychlorinated biphenyls (PCBs) onto soils and sediments limits their availability to PCB-degrading microorganisms. This availability to the biotic community, referred to as bioavailability, is an increasingly important component in the bioremediation of hydrophobic compounds. In addition, co-contaminants, such as fossil fuels, may substantially contribute to the organic component of the soil matrix, and result in a change in the sorptive behavior of PCBs. Researchers have demonstrated that both natural organic matter and residual oil components of soil act as a partition media for organic solutes such as PCBs, with the latter being roughly ten times more effective as a sorptive phase. In addition, studies have demonstrated the inhibition of degradation in the presence of a mineral oil component.

Our studies are focusing on environmental sites that are contaminated with both PCBs and fossil fuels. We have begun to enrich for microorganisms capable of biodegrading the fossil fuel fraction from several of these sites. In addition, we are isolating and characterizing pure cultures from these enrichments and assessing their individual contributions to fossil fuel biodegradation.

Milestones and Products for Year 3

1. Two Ph.D. students--Samuel Rawlin and Romish Stanislaus-- are continuing their doctoral research in my laboratory. Romish is studying a fossil fuel-degrading enrichment culture, and isolating microorganisms in pure culture from these enrichments. Six isolates have been partially characterized, and we are now studying the ability of the individual isolates to degrade a weathered crude oil. Samuel is acquiring literature on different methodologies to study the hydrophobicity of bacterial cells and the partitioning of non-polar contaminants into bacteria. We are conducting hydrophobicity tests on heterotrophic microorganisms isolated from a PCB-contaminated soil, by comparing their affinity for a hydrophobic phase (hexadecane). In addition, we are beginning to assess the potential of our isolates for biosurfactant production by observing changes in surface tension.

2. Obtained a permit from the National Park Service to collect soil samples for microbial inoculum from the future Aquarium site in Charleston. We have initiated enrichment studies for microorganisms from this soil that have fossil fuel-degrading capabilities.

3. Dr. Jim Mueller visited the laboratory, and presented a seminar for the Environmental Studies seminar series.

   - Oral presentation by Morris, P.J., Shelton, M. E. and Chapman, P. J. "Biodegradation of Polychlorinated Biphenyls and Fossil Fuel Co-Contaminated Soil and Sediment." American Society of Agronomy, Annual Meetings, Seattle, WA., Nov. 13-18, 1994. (91)

   - Poster presentation by Stanislaus, R., Shelton, M. E. and Morris, P. J. "Isolation of Fossil Fuel-Degrading Microorganisms." Abstract submitted to the American Society of Microbiology, May 1995 Annual Meetings, Washington, D.C. (92)

4. Roberto Frontera-Suau, a Ph.D. student, joined Samuel Rawlin and Romish Stanislaus in conducting doctoral research in my laboratory. Romish is studying a fossil fuel-degrading enrichment culture, and has isolated six microorganisms in pure culture from this enrichment. He is studying the ability of the individual isolates to degrade crude oil. Roberto Frontera-Suau has partially characterized the isolates. In addition, Roberto has conducted antibiotic susceptibility tests on 22 antibiotics in order to develop a screening method to monitor population dynamics during crude oil biodegradation. Samuel Rawlin is conducting hydrophobicity tests on heterotrophic microorganisms isolated from a PCB-contaminated soil, by comparing their affinity for a hydrophobic phase (hexadecane). He has observed that changes in nutrient concentration, from higher to lower levels, result in certain microorganisms responding as more hydrophobic in the assay.

5. Continued to examine crude oil-degrading enrichment cultures from several sites in the Charleston area--aquarium site, Washington Street Park, Calhoun Street, and James Island--and are in the process of characterizing the microorganisms from these cultures.

6. In January Romish Stanislaus and I traveled to visit Dr. P.S.C. Rao at the University of Florida's Department of Soil and Water Science to begin collaborative studies on techniques/methods to enhance the desorption of polychlorinated biphenyls and fossil fuels from contaminated soil. Romish will be returning in the summer to learn soil column chromatography techniques.

7. Gave an oral presentation based on the manuscript--Morris, P.J., M.E. Shelton, and P.J. Chapman, "Co-contaminated sites: The Biodegradation of Polychlorinated Biphenyls and Fossil Fuels" at Battelle's In Situ and On-Site Bioreclamation, the Third International Symposium, April 24-27 in San Diego, CA.

8. Gave a poster presentation based on the manuscript--Stanislaus*, R., M E. Shelton, and P.J. Morris, "Isolation of Fossil Fuel-Degrading Microorganisms" at the American Society of Microbiology Abstracts May 21 - 25 in Washington, D.C. (* Graduate student in my laboratory)

9. Gave a poster presentation based on the manuscript--Morris, P.J., M.E. Shelton, T.J. McDonald, and P.J. Chapman, "Extensive Biodegradation of Fossil Fuels Extracted from Soil and Sediment" at the Applied and Environmental Biology Gordon Conference July 2-7 at the New Hampton School in New Hampton, NH.

10. In June, a new student, Allison Stack, began studying the effects of biosurfactant production on surface tension by six microorganisms isolated from a fossil fuel-degrading enrichment culture.

11. Dr. Lucille London of MUSC's Dep ·ment of Microbiology and Immunulogy, and I began to co-sponsor two students (Arthur Jones and Sonya Ard-Kelly) on the undergraduate research program (running June - August). They are studying the effect of the biodegradation of contaminants on immunotoxicological response.

Milestones and Products Projected for Year 4

1. Will submit the following manuscript: Morris, P.J., M.E. Shelton, T.J. McDonald, and P.J. Chapman, "Extensive Biodegradation of Fossil Fuels Extracted from Soil and Sediment." Environmental Science and Technology.

2. Will have three Ph.D. students (Samuel Rawlin, Romish Stanislaus, and Roberto Frontera-Suau) conducting their dissertation research in the laboratory.

3. Will host a Department of Microbiology and Immunology Ph.D. student, Dan Bost, for a rotation in my laboratory. His project will focus on the biodegradation of polychlorinated biphenyls in a fossil fuel matrix.

4. Will prepare, submit and publish a manuscript on the biodegradation of saturated biomarkers (e.g. hopanes) found in crude oil by a microbial enrichment culture.

- Copy of paper

5. Will assist my three graduate students in preparing, submitting and publishing abstracts for the 1996 American Society of Microbiology Annual Meeting.

   - Copies of abstracts

6. Will complete research on the carbon source utilization pattern of *Phyllobacterium rubiacearum*, which is a gram negative microorganism capable of co-metabolizing the aliphatic hydrocarbon fraction of crude oil during growth on ammonia.

7. Will prepare, submit and publish paper on the characterization and carbon source utilization pattern of a *Phyllobacterium* strain isolated from a crude oil-degrading enrichment culture.

   - Copy of paper

5.1.8 Molecular Dosimetry in Reactive-Oxygen Species (ROS)--Mediated Toxicity of Environmental Chemicals.

Project Director:	James S. Norris, Ph.D.
Co-Investigators:	David Jollow, Ph.D.
	JoEllyn McMillan, Ph. D.
	David Kurtz, Ph.D.
	Steven Frawley, Ph.D.
	Inderjit Singh, Ph.D.

Executive Summary

Trichloroethylene (TCE) is a widely used industrial solvent that has pervasively contaminated the environment. At some hazardous waste sites, it is so concentrated that it has entered the ground water, soils and sediments to levels, thousands to millions of times higher than EPA regular maxims allow.

TCE toxicity is mainly targeted toward the liver. It has been shown in the B-6C3F1 mouse model to be a hepatic carcinogen. TCE exposure also induces lymphomas in hamsters, lung tumors in ICR rats and renal tumors in fisher 344 rats. However, there is some discrepancy between the consistency with which these tumors are observed among other rodent species and strains suggesting that there is a genetic element underlying susceptibility.

TCE is believed to function as a peroxisome proliferator. This has been demonstrated in rodent models but remains to be determined in humans. Peroxisome proliferators are typically able to act as hepatic carcinogens by mechanisms that are not well defined. For example, direct DNA damage by the compound has not been observed. However, the sensitivity of the assays used are not always sufficient to detect rare but predicted DNA damage that would be induced by this type of carcinogen via its ability to induce hydrogen peroxide in peroxisomes. Because peroxisome proliferators interact with their cognate receptors that interact with other receptors, it is also quite possible that TCE may act to alter transcription of important control elements in the cell. This latter activity, for example, induction of the oncogene might lead to chromosome instability and hepatic cancer.

In the proposed project, TCE will be evaluated for its peroxisome proliferation activity as well as for its ability to generate oxygen free radicals and corollary DNA damage. The system that we have available for doing these assays is state-of-the-art and will allow the assay to be carried out in a continuum in a single cell, providing the first direct functional information relative to oxygen free radical induction versus DNA damage. This project is groundbreaking in this respect and its future potential for analyzing mechanistic responses to environmental chemical exposure is considered highly significant.

Note on terms

An oncogene is a hypothetical viral genetic material carrying the potential of cancer.

Objective

To determine whether TCE or its metabolites induce free radical generation in the peroxisomes of established and primary human liver cells as primary cultures.

Milestones and Products for Year 3

1. Initiated construction of fos-luciferase (fos-luc) reporters, sequence, and checked functionality by transient expression approaches following stimulation with phorbol esters (control) and TCE metabolites (test).

2. Initiated testing fos-luc vectors in Dr. Frawley's photon counting apparatus under conditions (established above) where vector expression is observed.

3. Initiated establishment of conditions for photon counting that will later be analyzed for suitability in the comet assay.

4. All of the above experiments were and will be done in established cell lines. Once conditions are worked out, experiments will be repeated in primary rat hepatocyte cultures obtained from Dr. JoEllyn McMillan.

Milestones and Products Projected for Year 4

1. Will continue construction of fos-luciferase (fos-luc) reporters, sequence, and check functionality by transient expression approaches following stimulation with phorbol esters (control) and TCE metabolites (test).

2. Will continue testing fos-luc vectors in Dr. Frawley's photon counting apparatus under conditions (established above) where vector expression is observed.

3. Will continue to establish conditions for photon counting that will later be analyzed for suitability in the comet assay.

4. Will continue all of the above experiments in established cell lines. Once conditions are worked out, experiments will be repeated in primary rat hepatocyte cultures obtained from Dr. JoEllyn McMillan.

5.1.9 Immunogenetic Epidemiology of Scleroderma	
Project Director:	Janardan P. Pandey, Ph.D.
Co-Investigators:	Richard M. Silver, M.D.
	Susan Sutherland, Ph.D.
Graduate Student:	Paul Nietert
Laboratory Technician:	Phillip Werner

Executive Summary

Scleroderma (SSc) is an autoimmune disease characterized by inflammation and fibrosis of the skin and visceral organs. A number of occupational and environmental exposures have been related to the occurrence of SSc and SSc-like illnesses. Exposure to trichloroethylene (TCE), perchlorethylene, methylene chloride, trichlorethane, and other organic solvents has been reported in association with SSc. Thus far, there has been no epidemiological study conducted to investigate any relationship between SSc and environmental exposure to agents such as TCE.

According to the Agency for Toxic Substances and Disease Registry (ATSDR), about 400,000 workers are exposed to TCE in the United States during an average 40-hour work week. Moreover, TCE is widely used as a solvent and is used to make other chemicals and is found in typewriter fluid, paint removers, adhesives, and spot removers. We are conducting a case-control

study which will quantify the association between TCE exposure and SSc. A questionnaire has been developed and is being utilized to collect information on demographic characteristics, occupational histories and environmental factors from each SSc patient and control subject. Data collected through this questionnaire will help determine the relative risk of SSc due to TCE exposure.

Segregation analysis of several autoimmune families has shown that autoimmunity is controlled by a single autosomal dominant gene. The resultant autoimmune disease, if any, is probably determined by epistatic interactions of this primary gene with other secondary autoimmune genes and environmental factors. HLA class II, TNFα, IL-1α and β, GM, and KM loci are excellent candidates for the postulated secondary autoimmune genes, which could trigger the autoimmune disease state such as scleroderma. HLA class II alleles have been shown to be associated with susceptibility to several autoimmune diseases, including scleroderma. TNFα, IL-1α and β are important in several immunological activities and are mediators of inflammatory responses. TNFα has been shown to be a risk factor in some autoimmune diseases, e.g. SLE. Similarly, GM and KM loci have been implicated in a number of autoimmune disorders. In addition to these genes of the immune system, we will also study polymorphic loci that encode the major P450 (2E1,2B1/2,2C11/6) enzymes involved in the bioactivation of TCE.

Unlike some other autoimmune diseases, autoantibodies in scleroderma appear to be specific to this disease. Moreover, different autoantibodies are associated with different subsets of the disease. For example, autoantibodies to topoisomerase I (Scl-70) are found in patients with diffuse cutaneous SSc with a propensity to develop rapid and significant visceral disease. The limited cutaneous form of SSc (also known as the CREST syndrome) is associated with anti-centromere antibody (ACA) production. The significance of these autoantibodies in the pathogenesis of the disease is not understood.

We hypothesize that exposure to TCE increases the risk of SSc, and the host genetic factors--either through their effect on the immune system and/or by mediating the bioactivation of TCE--modify this risk.

Whereas the Medical University of South Carolina has: 1) 400 scleroderma patients and 52% thereof are SC residents; 2) MUSC survey research center; and 3) immunogenetic markers currently determined by MUSC immunologists and consultants, particularly within EHAP, MUSC is the proper place to conduct this project.

Objectives

1. To determine the prevalence of TCE exposure among scleroderma patients; to estimate the magnitude of the association between TCE-exposure and scleroderma; and to quantify the risk of scleroderma attributable to TCE.

2. To compare the distribution of immunogenetic markers (HLA, TNFa, GM, KM, IL-1a and b) among TCE exposed scleroderma patients with (a) non-exposed (idiopathic) scleroderma patients and (b) non-scleroderma controls.

3. To compare the distribution of the genetic markers of the major P450 (2E1,2B1/2,2C11/6) enzymes involved in the bioactivation of TCE among TCE exposed scleroderma patients with (a) non-exposed (idiopathic) scleroderma patients and (b) non-scleroderma controls.

4. To determine the gene-environment interaction effects of the genes of the immune system, genes regulating the bioactivation of TCE, and TCE exposure in scleroderma.

5. To determine the prevalence of scleroderma specific antibodies: anti-topoisomerase I (anti-Scl-70), anticentromere, and anti-RNA polymerase I, in idiopathic versus TCE -exposed patients.

6. To compare the association of autoantibodies with the genetic markers among TCE-exposed and nonexposed scleroderma patients.

Milestones and Products for Year 3

1. We have an IRB-approved consent form and our graduate student, Paul Neitart, collected data (questionnaire and blood specimens) from subjects in the Rheumatology Clinic and the Medical University Hospital. Thus far, we have collected data and blood from 63 patients and 33 control subjects. Blood samples from these subjects have been mailed to Dr. Yunis (Harvard Medical School) for HLA-DP, DQ, and DR typings. Determinations of other immunogenetic markers, RFLPs of the P450IIE1 gene, and the measurement of anti-Scl-70 autoantibodies are being carried out in our lab at MUSC.

2. Dr. Mustafa Dosemeci, from the Environmental Epidemiology Branch at the National Cancer Institute, consulted with us on April 12 and 13, 1995. He provided us with an overall critique of the project proposal. He suggested several changes to enhance the strength of the proposal,

including modifications to the questionnaire designed to collect individual risk factor information. Dr. Dosemeci also gave a presentation on the current methodology used to quantify individual exposure to TCE. This methodology is a necessary component of the proposal, and Dr. Dosemeci confirmed his willingness to collaborate in this investigation and continue to share his expertise. Dr. Dosemeci's experience in industrial hygiene is extensive, and his talents and experience will be great assets to our project.

3. Continued to determine the role of the genetic markers of κ light chains in an immune-mediated infectious disease--onchocerciasis, and a manuscript was produced as result thereof. Pandey JP, Elson LH, Sutherland SE, Guderian RH, Araujo E, Nutman TB: Immunoglobulin κ Chain Allotypes (KM) in Onchocerciasis. *Journal of Clinical Investigation* (Submitted), 1995.

   - Copy of manuscript (93)

Milestones and Products Projected for Year 4

1. Will continue to research the association of scleroder ·ith occupational and environmental exposures and chara .ze the prevalence of TCE exposure among a subset of scleroderma patients and controls.

2. Will explore collaborative arrangements with Dr. Chester Alper of Harvard Medical School to study the distribution of various complotypes in our subjects.

3. Will consult and explore collaborative arrangements with Dr. Flockhart of Georgetown University, an expert on the P450IIE1 gene.

4. Regarding the genetic susceptibility to scleroderma, we will determine the distribution of the following genetic markers among TCE exposed scleroderma patients with (a) non-exposed (idiopathic) scleroderma patients and (b) non-scleroderma controls: HLA DP, DQ, and DR; IL-1α, β, and TNFα alleles; genetic markers of P4502E1 enzyme; and GM and KM alleles.

5. Concerning the autoimmunity in scleroderma, we will determine the prevalence of the following antibodies in idiopathic versus TCE-exposed patients: anti-topoisomerase I (anti-Scl-70) antibodies; anticentromere antibodies; and anti-RNA polymerase I antibodies.

5.2 Risk Assessment Projects

5.2.1 Low Dose-Rate Radiation Health Effects

Project Director:	David G. Hoel, Ph.D.
Research Associate:	Zhen Zhang, Ph.D.
Research Associate:	Ping Li, Ph.D.
Graduate Student:	Tomas Radivoyevitch

Executive Summary

In the evaluation of external ionizing radiation exposure to man, all of the health risk assessments are based on acute exposures. It has been known from animal studies that often times for same total dose, the toxic effects of radiation are less if the exposure is given continually at a low dose-rate. Estimates of the reduction in risks have ranged from a factor of two to ten. Obviously, this would greatly impact the strategies for cleanup of radioactive materials and the level of permissible exposure to workers. This is particularly important because of the recent comparisons being made between A-bomb survivors and nuclear worker populations. The shape of the cancer dose-response function is also important to study in light of the discussion concerning hormesis. Hormesis is the stimulating effect of sub inhibitory concentrations of any toxic substance on any organism.

In studying exposure to workers, methods of physiologically based pharmacokinetic (PBPK) modeling and simulation are often used in dose-response evaluations of human health effects. Specifically, the project will utilize PBPK modeling and simulation to measure the effects of radiation in the body over time. Fate-transport models are used to estimate the distribution of radioactive materials in the environment including living and working places. In both cases, models are often highly nonlinear in nature and of a large number of variables and parameters. These models are usually developed with very limited information on the precision of the estimated input variables and model parameters.

Objectives

1. To determine dose-rate effectiveness factors for various cancers in rodent studies after gamma or neutron exposure.

2. To determine relative biological effectiveness of neutrons in rodent cancer studies and relate the rodent models to human epidemiological data.

3. To incorporate the analytical tools of systems science and engineering to the theoretical and methodological research of PBPK models.

Strategy

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

To examine the low-end of the dose-response function, cell cultures will be irradiated and mutations will be measured in real time through the use of the luciferase gene. Monte Carlo techniques and other methods such as calculation of sensitive indices are currently used for the evaluation of precision in human exposure estimation and dose-response analyses. We would like to develop a new method for the analysis of sensitivity based on global optimization search algorithms. The new method will be more suitable for nonlinear models of large number of estimated input variables and/or parameters.

Milestones and Products for Year 3

1. Completed expansion of connective tissue models to include a linear-quadratic dose response term. The dose rate effectiveness factor (DREF) becomes dose dependent.

2. Graduate student worked on compilation and comparison of existing methods. Completed initial programming work in Monte Carlo simulation and submitted a preliminary report (in revision).

3. Completed preliminary computer programming work and ready to test the new sensitivity analysis method on nonlinear fate-transport/exposure estimate models.

4. Re-modeled connective tumors and plots of the relative risk functions versus age of the mouse generated.

    - Two and three dimensional plots (94)

5. Fitted the major connective tissue tumor (lymphoreticular) using the linear risk model.

6. Lung tumors have been re-modeled and plots of the relative risk functions versus age of the mouse have been generated. A set of two and three dimensional plots are being submitted to EHAP. Plots are an estimation of dose-rate-effectiveness factors of both gamma and neutron.

    - Lung tumor plots (95)

7. Lymphosarcoma plots have been completed. Plots are an estimation of dose-rate-effectiveness factors of both gamma and neutron.

    - Lymphosarcoma plots (96)

8. Presented preliminary work on search algorithm-based model sensitivity analysis at the Annual Meeting of the Society for Risk Analysis in Baltimore in December 1994.

    - Copy of presented material (97)

9. Used multi-stage models to compare expected outcomes for acute and chronic exposures. Comparisons were made to show theoretical dose-rate effects that depended on what stage the radiation acted. The results will be incorporated into a future manuscript on dose-rate effects and used to compare with modeled animal dose-rate data.

10. Re-analyzed connective tissue tumors with improved model fits. These new models will be used to estimate the dose-rate effects and be compared with the predicted multi-stage model results. Remodeling allowed for the incorporation of a quadratic does term, which improved on the linear dose response fits that were done last quarter.

11. Obtained the following preliminary lab information: The Yeast Gall/Luciferase plasmid pJM400 from Dr. C. Nombela of Madrid, Spain. The plasmid was amplified in *e.coli* and used to transform the yeast strain 338 of Dr. J. Dolan at MUSC. The two transformed colonies were picked and grown in each of the three sugars, glucose, raffinose, and galactose. Luciferease activity was measured in a luminometer both before and after a two hour luciferase induction period. One of the colonies (Colony 2) showed a 10,000 fold increase in photonic activity over the control cells in galactose and a 1,000 fold increase in activity compared to the same cells grown in raffinose and glucose. The results indicated that the plasmid was successfully integrated into the yeast and that the luciferase enzyme was highly expressed under appropriate conditions.

12. Developed preliminary models that relate double strand breaks, repair error rates and radiation dose rates. Simulation studies of the models have begun. Completed reports describing the model and initial results.

    - Copy of reports (98)

13. Completed rodent tumor dose-rate study and a preliminary theoretical analysis using the Armitage-Doll multistage model. This work focused on what one expects from changes in dose-rate based solely on models considerations. Completed draft report.

    - Copy of report (99)

14. Completed redesign of a PC/windows based PBPK modeling and simulation software. The software allows an end-user such as a toxicologist to graphically design and define a PBPK model. Paper completed and ready for submission.

    - Copy of paper (100)

15. Dr. David G. Hoel continued to act as project director for the International Risk Assessment/Risk Management Forum. In this role, Dr. Hoel serves as primary liaison between the Medical University, the U.S. Department of Energy and the project's Steering Committee. The International RA/RM Forum will identify and present those European RA/RM practices that may be applicable in the United States. EHAP reports on this project in more detail in the Program Management section of this document.

Milestones and Products Projected for Year 4

1. Will model combined fitted dose rate effectiveness (DREF) data with theoretical results. Will produce manuscript

    - Copy of manuscript

2. Will complete low dose cellular model of double strand DNA breaks. Will complete a report and draft manuscripts.

    - Copy of report

    - Copy of manuscripts

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

Executive Summary

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.

This program is designed to be a major resource for decision makers involved in environmental remediation and restoration of hazardous waste sites. Furthermore, the project will provide timely feedback of community and population-based findings to concerned parties, in particular the risk assessment programs.

Objectives

1. To build and maintain a comprehensive survey research center for conducting population health, awareness, knowledge and perception assessments.

2. To develop methodology and implement the measurement of knowledge, awareness and attitudes with regards to environmental hazards risks to human health.

3. To quantify these measures and construct a perceived risk index.

4. To estimate levels of acceptable risk in the population.

Milestones and Products for Year 3

1. Completed an assessment of Georgia and South Carolina State Legislators with respect to environmental health. The population assessment indicated a significant proportion of the Georgia and South Carolina residents contacted politicians regarding environmental issues. These results prompted an assessment of legislators in Georgia and South Carolina. In general, legislators consider their constituents as "concerned" about environmental issues but received a relatively low number of comments from them.

- Technical report (101)

2. Completed an analysis of risk perception variation by race. Population risk perceptions vary by race as well as by geographic proximity to an environmental hazard source. The Risk Perception Survey was analyzed by race and a technical report produced (included in the appendix). African-American households appeared to have greater concerns regarding hazards in their immediate environment. The identification of such concerns are important in considerations of "environmental justice."

   - Technical report (102)

3. Completed an assessment of cancer cases in small geographic areas. Cancer cases from the Savannah River Region Health Information System were mapped by zip code and by census block. These maps demonstrate the capabilities of the project to identify cancer patterns in the population. In addition to cancer cases, population demographics are available to the system.

   - Maps (103)

4. The consensus of the Perceived Risk Advisory Committee was to assess risk perception in small geographic areas. The proposed survey for this consideration involves populations residing in close proximity to different "environmental hazards." Eight sites will be proposed with 200 interviews completed at each site. The study design and instrument will be finalized at the winter meeting of the Advisory Committee.

   - Proposed survey instrument (104)

   - Proposed study design outline (105)

5. Project leaders began planning a meeting of the Perceived Risk Advisory Committee for the next quarter.

   - Proposed meeting plans (106)

6. Planned the second "Perceived Risk Survey" that will be completed in small geographic areas around the Savannah River Site including Fernald, Rocky Flats, Hanford, Oak Ridge, Pinewood, and Spartanburg. Target populations are residents of these areas. The assessment will involve the quantification of attitudes, perceptions, and knowledge

and awareness regarding the health and environment risk of their proximal areas. Completed the survey that will be used.

- Copy of survey (107)

- Copy of study plan (108)

7. Decided to postpone the meeting of the Perceived Risk Advisory Committee until completion of the survey. This decision is an effort to conserve resources and to allow the Committee to review the results and make recommendations for analysis and future directions.

8. Obtained the Computer Assisted Telephone Interview (CATI) system from the University of Wisconsin. This system will greatly enhance the operations and capabilities of the population assessment efforts. The system has been installed and will be used for the next survey.

9. Implemented the Computer Assisted Telephone Interview (CATI) system in the second "Perceived Risk Survey." The survey began in May and will complete interviews in populations proximal the facilities at the Savannah River Site, Fernald, Rocky Flats, Hanford, Oak Ridge, Pinewood, and Spartanburg. Two hundred interviews will be completed via random digit dialing.

   - CATI Survey Interview (109)

10. Presented the population assessment methodology used to measure population perception at the Institute of Health in Munich, Germany. The Germans propose to replicate our efforts.

11. Presented population assessment methodology to representatives of the Agency for Toxic Substances and Disease Registry at the meeting, "International Congress on Hazardous Waste" June 5-8. This discussion prompted a visit to Charleston.

12. Wrote technical report on geographic variation in risk perception.

    - Copy of report (110)

13. Produced a technical report on racial variation in risk perception.

    - Copy of report (111)

Milestones and Products Projected for Year 4

1. Will hold a regular meeting of expert advisory committee. The expert advisory committee will meet, review current work and recommend future activities.

    - Report of meeting

2. Will complete an assessment of small geographic areas and populations at risk. A population survey will be completed on small geographic areas to identify association with risk perception and to identify at-risk populations.

    - Technical report

    - Scientific publication

3. Will develop methodology to determine a population index of risk perception. Responses from population survey will be used to develop a "population index of risk perception".

    - Scientific publication

4. Will identify population attributes that contribute to environmental risk perception. Responses from population survey will be used to identify population characteristics associated with risk perception.

    - Scientific publication

5. Will use resources to complete population assessments. The resources developed for population surveys could be used to conduct population assessments,

    - Survey responses

6. Will complete population assessments around multiple DOE sites. Surveys will be completed around multiple DOE sites to provide baseline comparisons of perception, attitude and behavioral characteristics of the different populations.

    - Scientific publication

5.2.3	The Development and Implementation of a Geographic Analysis System for Population Health and Environmental Risk Assessment	
Project Leaders:		Daniel T. Lackland, Ph.D. John Dunbar, Dr. P.H. David G. Hoel, Ph.D.

Executive Summary

Traditional approaches for the assessment of environmental exposure evaluation have employed the usual screening methodologies. In a typical assessment, investigation will select a population believed to be at risk, collect data and tissue samples, and determine cases of exposure and potential adverse health outcomes. Although this approach is useful, numerous limitations exist. First, only individuals who are selected and agree to participate are used in the investigation. Risk assessment of specific geographic areas is very difficult as surrounding areas are not identified or assessed, and geographic clusters of events are often missed with one hundred percent participation. A second limitation involves the difficulty in obtaining often missing information on confounders in a high-risk population. Use of computerized data bases, such as census demographic files, water quality, tax records, and health records is extremely laborious to quantify and is typically completed variable by variable. In summary, the traditional assessment methodology is useful for the study of a single household, only cursory investigations are possible for large regions and populations.

An alternate and progressive approach is proposed which will utilize a geographic information system (GIS) to be used in the defining of geographic study areas and the analysis of multiple data sets. The proposed system will consist of computerized data bases structured to a defined geographic area combined with analytic tools including thematic map generation, proximity analysis, buffer zone identification, and map overlay comparisons.

Objectives

1. To complete and assess comprehensive geo-coding of all addresses and areas in a specific geo-political area.

2. To merge health, demographic and environmental data sets based on location in the geographic analysis system.

3. To complete a health and risk assessment on a defined geographic area.

Milestones and Products for Year 3

1. Completed pilot geo-coding of selected geographic areas. Charleston County was selected as the first pilot site for the geo-coding. By the end of August, 85% of the county had been geo-coded. Several census tracts were 100% complete as geo-coded areas. Efforts will be made to complete the coding of all areas in the cancer registry coverage area. A sub-contract for completion of these activities has been implemented with the Division of Research and Statistics.

2. Documented geo-coding methodology. The geo-coding process of selected areas of South Carolina was initiated in Year 3. The protocols and documentation are guided by the results of the pilot project efforts. Thus, final documentation is not complete. A sub-contract has been negotiated with the Division of Research and Statistics of the State Budget and Control Board to complete the production of the documentation of methodology. An abstract was submitted to 1995 CDC/ATSDR Symposium on Statistical Methods.

    - Abstract (112)

3. Established a contract with the Office of Research and Statistics of the South Carolina State Budget and Control Board. This collaborative arrangement will institute the first phase of the geo-coding and will provide an essential resource for population risk assessment.

    - Copy of contract (113)

4. South Carolina Budget and Control Board's Office of Research and Statistics delivered a report of activities and details of the contractual progress.

    - Copy of report (114)

5. Presented results of our geographic analysis system efforts at the DC/ATSDR Symposium on Statistical Methods: Small Area Statistics in Public Health--Design, Analysis, Graphic and Spatial Methods, January 25-26 in Atlanta. Received high visibility and attention for the presentation, "The Development and Implementation of a Geographic Analysis System for Population Health and Environmental Risk Assessment."

    - Copy of program (115)

6. Presented "Geo-coding of Health and Demographic Data as a Resource for Environmental Incidents Preparedness and Response" at the

American Nuclear Society Topical Meeting: Emergency Preparedness and Response, April 19-21 in Savannah, GA.

- Copy of manuscript (116)

7. Presented geo-coding methodology at the Institute of Health in Munich, Germany.

8. Discussed geo-coding methodology with representatives at the Agency for Toxic Substances and Disease Registry.

9. The Office of Research and Statistics continued to make significant progress at address matching.

   - Copy of report (117)

Milestones and Products Projected for Year 4

1. Will development of methodology to complete comprehensive geo-coding of geographic areas. The various priority areas will be geo-coded as described in contract with Office of Research and Statistics.

   - Regular reports on completed area

2. Merging of data sets to geo-coded areas. Various data sets will be mapped using the completed geo-coded areas. For example, disease endpoints, socio-economic status indicators, etc. will be mapped by demographics.

   - Scientific reports and presentations.

3. Calculation of rates using the merged data sets for geo-coded areas. Rates such as disease rate will be calculated and color-coded for presentations.

   - Scientific reports and presentations

4. Development of an analytical methodology to quantify and analyze the data in geo-coded area.

   - Scientific reports and presentations

5.2.4 Risk Assessment of Trichloroethylene

Project Director:	David G. Hoel, Ph.D.
Research Associate:	Zhen Zhang, Ph.D.
Research Associate:	Ping Li, Ph.D.

This project was not funded during the past quarter. As this report goes to press, the additional funding for this project requested from the Department of Energy has not been confirmed for First Quarter, Year 4.

Executive Summary

We propose to work towards developing a risk model for low-dose exposures to Trichloroethylene (TCE). This work will begin with a follow-up of the results of the PBPK work of ChemRisk and the Peer Review Panel. We shall carryout the following detailed evaluation of the use of the PBPK findings in a risk assessment followed by a linkage of these results to toxicological outcome data and model as well as any human health data.

Uncertainty Analysis of PBPK models of Trichloroethylene (TCE)

There is a considerable amount of knowledge available on the major metabolic pathways of TCE for a number of species. This facilitates the development of PBPK models of TCE for animals. However, the lack of adequate human data in many of the critical aspects of the modeling process will undoubtedly introduce uncertainty in the model end-point results of PBPK models of TCE for humans. In this project, we propose to utilize 1) a computational method based on "importance sampling"; and 2) systems analysis methods to identify potential sources to the overall model output uncertainty.

1) A Genetic Algorithm Based Importance Sampling Method for Sensitivity Analysis

Recently, there has been an increasing effort in applying Monte Carlo simulation methods for model sensitivity analysis. However, for non-linear models with a large number of input parameters, the limited number of simulation runs do not always adequately reflect the true properties of the underlying sample space. Improved sampling techniques may help to distribute the sample points more evenly over the entire space. They do not, however, solve the problem of having too few sample points in areas of importance. What is often of concern is the tail portion of the model end-point output distribution. However, for complicated nonlinear systems such as PBPK models, it is often an impossible task to identify regions in the high dimensional sample space that contribute to the tail portion of the output distribution. In our research, we have developed a computational method

based on the genetic algorithm (GA) optimization technique. In this approach, a user-specified evaluation function defines what is "important" in terms of the Monte Carlo simulation results. In some cases, it may be defined as having output close to the extreme end of the output distribution. The genetic algorithm then searches for points in the input parameter space (sample space) that minimized the evaluation function (e.g. distance to the theoretically possible extreme output value). During the process, a collection of sample points that are of "importance" in our sensitivity analysis are identified with a limited number of simulation runs. Statistical analyses are then performed to evaluate the relative sensitivity of input parameters.

2) *System Analysis Methods*

Systems analysis methods can be used to verify model stability and hence, to identify possible intrinsic or structural sources that might cause high model sensitivity. PBPK models are essentially a set of non-linear differential equations with parameters that are of physiological and/or anatomical interpretations. We should still be able to analyze such models with the traditional systems analysis methods. As an example, in our previous research, we have proved a set of conditions under which some of the organs or tissue regions may be "lumped" together without affecting the computation of concentrations in the remaining tissue regions. This can significantly simplify the analysis of model output sensitivity to parameter changes since the number of parameters is reduced.

Objective

1. To use new and advanced scientific methods to evaluate and improve current approaches to risk assessment of low-dose exposure to TCE for both carcinogenic and non-carcinogenic effects.

Milestones and Products Projected for Year 4

1. Will initiate review of PBPK work of ChemRisk Panel.

2. Will complete a literature review of sensitivity analysis for TCE PBPK models. Summary of current status in sensitivity analysis for TCE PBPK models will be produced.

   - Copy of summary

3. Will implement the TCE PBPK model with sufficient level of details using advanced simulation algorithms. Will utilize a software program for TCE PBPK model simulation using advanced paralleled processing algorithms.

4. Will implement the sensitivity analysis computer program using important sampling method and generic algorithm, and to accomplish this, we will utilize a software program for sensitivity analysis using important sampling methods and generic algorithm.

5. Will implement sensitivity analysis of input parameters and variables of TCE PBPK model using above mentioned software program systems.

6. Will utilize system analysis methods to simplify TCE PBPK sensitivity analysis. As a result, we will produce a manuscript describing developed methodology.

    - Copy of manuscript

5.3 Education

5.3.1 Graduate Education in Risk Assessment	
Project Director:	Dr. Rosalie Crouch, Dean, College of Graduate Studies
Assistant Director:	Dr. Eberhard Voit, Assistant Dean for Environmental Studies

Executive Summary

The educational component is an essential part of the environmental risk assessment program. This task concerns establishing strong academic graduate programs at the master's and doctoral levels addressing the needs of governmental agencies, private industry and public concerns. These programs 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 have, in addition, considerable expertise in a defined area that they select for their dissertation. In future years of the project, attention will be given to undergraduate environmental studies programs. These topics will also be introduced at the primary and secondary school levels.

Objective

To develop outstanding academic programs at the master's and doctoral levels that educate the student in the fundamentals of environmental risk, policy and science with a specialization in one of these areas.

Milestones and Products for Year 3

1. Dr. Eberhard Voit, Professor, Department of Biometry and Epidemiology, appointed Assistant Dean for Environmental Studies and charged with overseeing educational programs. Drs. Voit and Robert Dukes, Professor and Chairman of the Department of Physics at the University of Charleston, added to Master in Environmental Studies (MES) Program Steering Committee.

2. Teaching positions in risk assessment advertised in international journals. So far, 14 applications received by search committee.

   - Copies of advertisements (118)

3. Additional applications to MES program processed. A total of 14 students admitted to the program; one subsequently requested deferral to the Fall of 1995. Six additional students admitted to Ph.D. program in Biometry and Epidemiology with Emphasis in Environmental Risk

Assessment; two of these were admitted without EHAP stipend support.

- Lists of MES and Ph.D. students enrolled in Fall 1994 (119)

4. Advertisement and recruitment poster for MES program completed and printed. Mailing labels obtained from Peterson's Guide.

   - Poster (120)

5. Seminar Series in Environmental Studies initiated for Fall 1994.

   - List of invitees (121)

6. MES workshop held for strategic planning and further development of multi-disciplinary core courses.

   - Agenda (122)

7. By invitation, we presented MES and Ph.D. programs at the international Envirometrics Conference in Burlington, Canada. Additionally, Dr. Eberhard Voit, in collaboration with Dr. W. Leonard Balthis, presented a slide show entitled "Assessment of Size-Dependant Mercury Distributions in King Mackerel."

   - Copy of slides re: MES and Ph.D. Programs (123)

   - Copy of slides re: mercury distributions (124)

8. Held a Summer Undergraduate Research Program, which allows interns to do research in environmental studies. Ten outstanding students were accepted to and completed the program. A volume describing the program and their projects was published.

   - Copy of book (125)

9. Advertised risk assessment teaching positions in international journals. To date, have received 45 applications.

   - Detailed list of applicants (126)

10. Additional applications to Masters in Environmental Studies (MES) program were processed. A total of five students were accepted to the program for the Spring 1995 semester, bringing the total number of students to 16.

- Lists of MES applicants accepted for the Spring 1995 semester (127)

11. Received 265 requests for information from recruitment posters. Of these, 135 have requested applications.

    - Chart of requesting students, broken down by state and scientific background (128)

10. Finalized the Seminar Series in Environmental Studies for the Fall 1994 semestér.

    - Confirmed list of speakers (129)

12. For fall 1995, advertised risk assessment teaching positions in international journals. Received 57 applications to date.

    - Detailed list of applicants (130)

13. Processed additional applications to MES program. Received 32 applications for Fall 1995. From these 32, 20 have been accepted with 11 still being reviewed.

    - List of MES applicants accepted for Fall 1995 (131)

14. Received 985 requests for information since September.

    - Chart of requesting students with requests from posters broken down by state and scientific background (132)

15. Finalized plans for Spring 1995 semester's Seminar Series in Environmental Studies.

    - List of guest speakers for spring semester (133)

16. Filled teaching position in Risk Assessment. An offer was extended to Dr. Nicholas Lawryk on April 22.

17. Processed additional applications to MES program. Received a total of 41 applications for Fall 1995. From these 41 applications, 30 applicants have been accepted to the program with six awaiting review. Four additional students admitted to Ph.D. program in Biometry and Epidemiology with Emphasis in Environmental Risk Assessment.

    - Lists of MES applicants accepted for Fall 1995 and status sheet and list of new Ph.D. students (134)

18. Received 1,319 requests for information since September 1994. 765 are from recruitment posters, 196 are from telephone inquiry, 25 from brochure return card, 19 written requests, and 314 were forwarded from the University of Charleston. Applications requested from all sources was 715.

    - Chart of requesting students with requests from posters broken down by state and scientific background (135)

19. A new course, Environmental Epidemiology, was initiated for the summer. The course has nine students enrolled.

    - List of students enrolled in course and course announcement (136)

20. Developed new course, Environmental Immunology, which will begin in the fall. The instructors are Dr. Karen Burnett and Dr. Robert Galbraith.

    - Course announcement (137)

21. Developed Case Studies Course and submitted to the Curriculum Committee for approval.

    - Course description submitted for approval (138)

22. Enrolled three students in summer internships.

Milestones and Products Projected for Year 4

1. Will enroll 30 or more students in the Masters in Environmental Studies Program.

    - List of Students

2. Will enroll 4 additional Ph.D. students with emphasis in Environmental Health Risk Assessment.

    - List of Students

3. Will extend course offerings in the areas of: a) exposure assessment; b) environmental epidemiology; c) occupational health; d) ecological risk assessment and e) environmental immunology for MES students and for Ph.D. students with emphasis in Environmental Health Risk Assessment.

4. Will develop opportunities for summer internships.

- List of Students enrolled in internship

5. Will develop additional strategies of student recruitment to MES and Ph.D. programs.

6. Will offer seminar series in Environmental Science.

   - List of Seminar Speakers

7. Will offer Summer Undergraduate Research Program in Environmental Science; place emphasis on minority recruitment.

5.3.2 Department of Health Administration and Policy	
Project Director:	David R. Graber, Ph.D.
Chairman and Professor, Department of Health Administration and Policy:	James Johnson, Ph.D.

Executive Summary

Continuing responsibilities during Year 3 were in three major areas: environmental health policy, environmental health education, and international environmental issues. This program also implements research projects involving the extent to which considerations (other than purely scientific ones) are incorporated into environmental decision-making. These may include social and economic considerations, as well as citizen participation issues. A major thrust of the Policy Studies Journal symposium, the hazardous waste study, and future planned projects will address the relations of social and economic issues and environmental policy.

One major milestone was achieved with the completion of the study on perceptions of hazardous waste operators and inspectors. A paper and presentation on comparative views of hazardous waste site operators and inspectors was prepared for the National Association of Environmental Professionals' June meeting in Washington, DC. This product is part of an over-arching effort to increase understanding of and to improve policies for the management of hazardous waste. As a result of this project, a number of recommendations were developed for improved regulatory policy and operations of hazardous waste sites.

Objective

1. To analyze and assess the current status of environmental medicine and education in American medical schools.

2. To assess the interrelation to the environment of agricultural activities in Third World countries.

Milestones and Products for Year 3

1. Completed research on the attitudes of medical school academic deans on environmental health curricula.

    - Paper by Graber, D., and Musham, C. "Environmental Medicine Education in the United States." Forthcoming in the Journal of Environmental Education, Fall, 1994. (139)

2. Completed a study of the impact of agriculture on the environment and the effect of environmental factors on farmer health and well-being. Five principal dimensions of the agriculture/environment interrelation were assessed: water resources; erosion and non point source pollution; pesticides and fertilizers; deforestation; and biodiversity.

    - Article written by Graber, D., Johnson, J., and Jones, W. Human and Ecosystem Health: the Environment - Agriculture Connection in Developing Countries. Submitted to the Journal of Ago-Medicine, 9/94). (140)

3. Received nine articles from authors for Environmental Health Policy Symposium Issue of *Policy Studies Journal*. Submitted articles to journal editors for revisions/review prior to publication.

4. Finished statistical analysis of hazardous waste site operators and regulators data. Compared and contrasted views and recommendations of survey respondents. Also, completed paper with co-authors on environmental health in medical school curricula. Wrote and submitted articles.

    - Manuscript by Graber, D. "Views of Operators and Inspectors of Hazardous Waste Sites." Published by the Environmental Management Review, Winter 1994. (141)

    - Manuscript by Graber, D., Musham, C. Bellack, J., Holmes, D., "Environmental Health in Medical School Curricula: Views of Academic Deans." Journal of Occupational Medicine. Accepted for publication in spring 1995. (142)

- Manuscript by Graber, D., and Johnson, J. "Obstacles to Hazardous Waste Minimization." American Public Health Association. Annual Meeting. October 1994. (143)

5. In November 1994, finished preparation for spring 1995 course at MUSC in Environmental Health Policy. Contacted guest speakers on topics such as air, water, and hazardous waste policy.

6. Completed paper "Perspectives on Environmental Health Policy" for inclusion in Policy Studies Journal.

   - Copy of paper (144)

7. Completed data analysis and wrote abstract and paper "Hazardous Waste Site Operators and Inspectors: Their Perceptions of the Media and Environmental Groups." Submitted to National Association of Environmental Professionals.

   - Copy of paper (145)

8. Taught course in Environmental Health Policy at MUSC in spring 1995.

9. Initiated preliminary data analysis for two abstracts "Environmental Clusters and Ranking of Selected Nations" and "An Organizational Typology of Environmental Agencies and Businesses." These have been submitted for presentation at the October 1995 American Public Health Association Meeting in San Diego.

   - Copy of abstracts (146)

10. Presented a paper by Bellack, J., Musham, C., and Graber, D., "Environmental Health Competencies: A Survey of U.S. Nurse Practitioner Programs" at Southern Nursing Research Society Annual Conference on February 17.

12. Began initial compilation of database of international environmental indicators (e.g., hazardous waste, toxic substances, air/water pollution, greenhouse gases, deforestation).

13. Published Environmental Health Policy Symposium Issue of Policy Studies Journal. Journal edited by D. Graber and J. Johnson, and article co-authored by D. Graber.

    - Copy of journal (147)

14. Attended and presented abstract to National Association of Environmental Professionals in June 1995.

    - Copy of conference proceedings (148)

15. Continued preliminary data analysis for two abstracts submitted for presentation at the October 1995 American Public Health Association Meeting in San Diego. Abstracts accepted for presentation at APHA meeting: A) Environmental Clusters and Ranking of Selected Nations. B) An Organizational Typology of Environmental Agencies and Businesses.

    - Copies of abstracts (149)

Milestones and Products Projected for Year 4

1. Will edit a book on environmental health policy. D. Graber and M. Jones will serve as the editors.

2. Will give two conference presentations at the October 1995 American Public Health Association Meeting in San Diego. Will produce two published abstracts.

    - Copies of abstracts

3. Will write paper for winter, 1996 issue of New Solutions on "Hazardous Waste Management."

    - Copy of paper

4. Will teach course in Environmental Health Policy in Spring 1996.

6.0 CLINICAL PROGRAMS

6.1	Health Services Research
Project Director:	W. Allen Smith, Dr., P.H.

Executive Summary

Health Services Research has been involved with EHAP and risk assessment since the grant was initiated, but before the first quarter of year three, the project's mission was carried out under Program Management. In accordance with the new emphasis placed on involving medical doctors and other medical practitioners in the environmental risk assessment and decision-making process, Health Services Research continues to be a separate project.

Through personal networking, I have been meeting with numerous MUSC faculty members to explain in detail the concept of risk assessment in medicine. As a result, many departments and individual physicians have taken an interest in the project, and many individuals have been recruited into health risk associated projects.

Additionally, I have participated in a conference that concentrated on predicting the mass tort cases of the future, and as a result and in collaboration with the Einstein Institute, the project may produce a videotape for the training of judges in environmental health issues.

Other plans include an industrial medicine clinic and a referral system, both of which would further institutionalize risk assessment in the practice of medicine. As the various elements of the project develop, more physicians, other medical practitioners, and assorted professionals will be better educated in environmental health issues.

Objectives

1. To involve more medical doctors and other medical practitioners in the environmental risk assessment and decision-making process.

2. To create a need-to-know attitude toward environmental medicine.

Milestones and Products for Year 3

1. Recruited Dr. Bill Simpson as Associate Medical Director of the Occupational and Environmental Medicine Office.

2. Participated in the Cassatt community meeting on August 3, 1994. One topic of discussion during the meeting was integrating the needs of the Cassatt community in rural Kershaw County, S.C. with the learning experiences of the students in the University of South Carolina College of Nursing and EHAP of MUSC. However, the primary focus was the concerns of the citizens regarding the Columbia Organic Chemical Site, which closed in 1991 due to violations of hazardous waste regulations. Many citizens from the community expressed concerns that their medical problems were related to the closed site. A difference of opinion was evident in that the S.C. Department of Health and Environmental Control implied a desire to act immediately while I and others advocated a study design that would avoid "dead end" results.

    - Copy of meeting notes (150)

3. Participated in the "Emerging Environmental Issues Conference" September 19- 20, 1994, which was held in Lake Geneva, Wisconsin. The focus of my participation was in predicting the mass tort cases of the future, and as a result and in collaboration with the Einstein Institute, the project may produce a videotape for the training of judges in environmental health issues.

4. Initiated, in association with the Environmental Medicine Curriculum Committee, the development of two of the eight modules of the elective curriculum.

5. Started planning for an industrial medicine clinic and a referral system.

6. Began planning a faculty/student reassessment of the Student Health Coalition project. This project represents a unique opportunity to introduce environmental medicine concepts into the undergraduate medical curriculum. This should be an exportable idea for achieving this otherwise difficult or unattainable goal.

7. Continued efforts in the Cassatt, SC, study with the addition of a graduate student from the USC School of Public Health. This is important because this is the first collaborative effort with the School of Public Health and its faculty.

8. Attended an American Public Health Association meeting with the specific purpose of evolving a working definition of environmental equity for our purposes. Synthesizing information from the meeting, I conclude that environmental equity is the process of empowering a community to take an active, informed part in approaching and solving their environmental health problems. The public can better

understand environmental equity by focusing on this issue with respect to people and communities and not as an economic or black/white issue, as some would advocate. It is notable, too, that this is the objective of our efforts in Blackville and Cassatt, SC.

9. Continued organizational efforts for reassessing the Student Health Coalition.

10. Participated in the first EHAP External Advisory Group Meeting.

11. Participated in the oral examination of our graduate student from the USC School of Public Health.

12. Tried on an experimental basis using the Student Health Coalition as a vehicle through which to inject OEM principles into the undergraduate medical curriculum. However, the ad hoc university committee to study the Coalition's future has found that the activity is redundant and that other activities more closely meet the medical school curriculum needs. While we shall continue to look for alternative ways to infiltrate the curriculum, it is probably true that student needs are best met at the graduate level.

13. Planned a joint faculty meeting to introduce Clemson to a variety of environmental health issues of concern to the medical community. There are benefits to be derived from bringing together the disciplines of medicine and engineering in environmental health. It is envisioned that a memorandum of understanding between MUSC and Clemson could result in the exchange of both faculty and students in medicine and engineering.

14. Work of the Family Medicine OEM curriculum committee produced a core curriculum and a number of elective educational modules. We are now looking for opportunities to export these modules and the techniques used in their development. We believe that the developmental technique and the process involved is probably more important than the actual modules regarding their effect upon the medical community's desire to learn and participate in environmental health issues.

15. Attended meetings of the Charleston Naval Base Redevelopment Authority because the Charleston Naval Shipyard could offer an opportunity for MUSC to take a leadership role in addressing the health hazards created by the departing military. Unfortunately, the closure and reuse of the base facilities has been in disarray, and our role at this time is a bit obscure.

16. Continued to plan the October 25-26, 1995 symposium, "The Environmental Risk Assessment: Does it Work for the Community-Based Family Physician?" This meeting of nationally recognized (practicing) family physicians will take place in Charleston, SC, and may stimulate interest and encourage greater participation among the primary care medical community in the discussion and resolution of environmental risk issues. Attendees will evaluate the utility of the current risk assessment processes to the family practice physician in his/her role as a community health advocate. They will also explore things that can be done to improve this utility.

Milestones and Products Projected for Year 4

1. Will continue to work toward hosting a meeting of nationally recognized (practicing) family physicians.

2. Will continue to look for opportunities for the Medical University to take a leadership role in addressing the health hazards created by the departing military at the Charleston Naval Base and Shipyard.

3. Will attend national and state meetings related to public health to facilitate a need-to-know attitude toward environmental medicine.

4. Will continue to look for ways to collaborate with the Einstein Institute in predicting the mass tort cases of the future, and as a result, try to produce a videotape for the training of judges in environmental health issues.

5. Will continue to work closely with the Occupational and Environmental Medicine (EOM) effort (project #6.2 below) to determine how the core and elective curriculum modules should be disseminated.

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

Executive Summary

Historically there has been little or no environmental and occupational medicine (EOM) training in the curriculum of family practitioners even though this group of physicians see more EOM patients than any other medical specialty. In addition, patients expect their family physician to be knowledgeable about environmental risks in their community. Family medicine residents and practitioners who receive training in EOM will be able to better serve their patients and community in the risk assessment process.

These needs led to the project goal of developing and implementing graduate and continuing medical education curriculum in EOM for family physicians. To achieve this goal, an Environmental Medicine Curriculum Committee (EMCC) comprised of at least one faculty member from each of the seven teaching sites of the South Carolina Statewide Family Practice Residency Program (SFPRP) was formed to advise the OEMO on curriculum development. The OEMO also developed an EOM resource to support the faculty, residents and staff of the Statewide Family Practice Residency System (SFPRS) with consultations on patients with EOM complaints. The work of the committee and EOM consultative resource is ongoing. Future activities include adapting the core and elective EOM curriculum to other disciplines and into self-study programs for the busy practitioner.

All activities during the past quarter proceeded on schedule. Sub-committees of the EMCC continued to work closely with OEMO staff in the development of the EOM elective curriculum slides and lecture notes. Project staff consulted on 48 EOM cases during the period and presented 14 EOM lectures. In cooperation with Dr. W. Allen Smith, project staff continued to develop plans for a national meeting of leaders in family medicine.

Objectives

1. To provide continued support to the Environmental Medicine Curriculum Committee (EMCC) including EOM consultative and research services to the Statewide Family Practice Residency System.

2. To develop eight environmental medicine elective curriculum modules for family medicine residents and to update core curriculum modules.

3. To determine if the core EOM curriculum can be adapted to other disciplines.

Milestones and Products for Year 3

1. During the Year 3, staff members consulted on 250 environmental/occupational medicine cases during the period. Cases were described in the July - September 1994 Summary Reports.

   - July - September 1994 Summary Reports (151)

2. Information and rotary file cards describing the consultative and case research services of the Environmental and Occupational Medicine Office were printed. These will be distributed to departments on campus. The informational card features the mnemonic WHACS to remind physicians to include an EOM history in the patient's chart. WHACS was developed by the EMCC and represents five key questions: 1) What do you do? 2) How do you do it? 3) Are you concerned about any of your exposures on and off the job? 4) Co-workers or others exposed? 5) Satisfied with your job?

   - OEMO information card (152)

   - OEMO rotary file card (153)

3. The EMCC met September 15-16 at the Sheraton Hotel and Convention Center in Columbia. Nine of 10 members attended and all seven teaching sites were represented. Additionally, one resident each from the Charleston, Greenville and Greenwood programs attended and advised the committee on residents' needs for EOM curriculum. The committee focused on the review and implementation of the EOM core curriculum modules and developing outlines for the elective curriculum. We will present the meeting agenda in the September *Environmental Medicine Update*. Meeting details will be published in the October issue.

   Macintosh interactive computer programs for the following EOM core curriculum modules were distributed to the EMCC on September 16:

   - Module 1-Environmental and Occupational Medicine History for Family Physicians (154)

- Module 2-Communicating Environmental and Occupational Risks to Patients: A Guide for the Family Physician (155)

- Module 3-Environmental and Occupational Medicine Resources for the Family Physician (156)

- Module 4-Environmental and Occupational Medicine in Private Practice: Choices for the Family Physician (157)

- Module 5-Using Hospital Site Visits for Teaching Environmental and Occupational Medicine (158)

4. The EMCC developed outlines for the following EOM elective curriculum modules:

   Low Back Pain and Carpal Tunnel Syndrome
   Noise Induced Hearing Loss
   Acute and Chronic Exposure
   EOM Dermatitis
   EOM Pulmonary Disease
   Impact of Substance Abuse in EOM
   Low Dose Exposures
   Workers' Compensation and other Legal Issues

5. The EMCC published its monthly newsletter, *Environmental Medicine Update*, from July -September 1994. The objectives of the newsletter are to report on the activities of the EMCC and to stimulate committee members concerning recent developments in EOM.

   - *Environmental Medicine Update* - Volume 1, Number 12 and Volume 2, Numbers 1-2. (159)

6. Presented 42 EOM lectures during the year.

7. The EMCC surveyed all alumni of the MUSC Department of Family Medicine. The objectives of this pilot study are to determine: 1) the extent of EOM in their practice; 2) suggestions for EOM curriculum improvements in residency training; 3) the need for EOM continuing medical education; and 4) the feasibility of the mail survey for the other six residency sites.

   - Summary Report - Charleston Family Medicine Survey for Environmental and Occupational Medicine, 1994 (160)

8. The southeast regional meeting of the Society of Teachers of Family Medicine (Sept. 16-18) featured the EOM core curriculum modules and

a poster on EMCC activities. EMCC member, Dr. Mark Godenick, was responsible for this activity.

9. Faculty representing the University of South Alabama, East Tennessee State University, and East Carolina University expressed interest in including the modules in their curriculum (disseminating the modules is a planned activity for the next project year).

10. Drs. Schuman and Simpson met with MUSC College of Nursing faculty on September 8 and 12. The objective of the meetings was to show the faculty the EOM core curriculum modules developed for family medicine residents and determine whether the modules could be adapted to the nursing curriculum. On September 22, Dr. Elizabeth Erkel advised Dr. Schuman that she and her colleagues would like to adapt the curriculum to their nurse practitioner program.

    - Memos documenting the initial meetings and an electronic mail message from Dr. Erkel confirming the nurses' interest. (161)

11. Continued to add monthly environmental and occupational medicine literature review for pertinent articles to the project's computerized data base.

12. At the September 15-16 EMCC meeting, members formed sub-committees to assist the OEMO staff in the development of the elective EOM curriculum. Draft slide lectures and scripts were completed in December and forwarded to the appropriate sub-committee members for review and comments.

    Sub-committee members: Dr. Grubbs and Dr. Rowe
    OEMO Leader: Samuel T. Caldwell
    Modules: Low Back Pain
    Carpal Tunnel Syndrome
    Noise Induced Hearing Loss

    Sub-committee members: Dr. Godenick, Dr. Schuman and Dr. Ruiz
    OEMO Leader: Larry H. Spell
    Modules: Acute and Chronic Chemical Exposure
    EOM Dermatitis
    EOM Pulmonary Disease

    Sub-committee members: Dr. Anderson, Dr. Simpson and Dr. Terrell
    OEMO Leader: Jan A. Lay
    Modules: Impact of Substance Abuse in EOM

Low Dose Exposures
Workers' Compensation and other Legal Issues

13. *Environmental Medicine Update,* the monthly newsletter, was published October-December 1994. Monthly Summary Reports were completed and published.

    - *Environmental Medicine Update* - Volume 2, Numbers 3-5. (162)

    - October-December Summary Reports (163)

14. Alumni of the Statewide Family Practice Residency Program were surveyed. The objectives of this pilot study are to determine: 1) the extent of EOM in their practice; 2) suggestions for EOM curriculum improvements in residency training; and 3) the need for EOM continuing medical education. In addition to completing a follow-up survey of its own alumni, the OEMO also surveyed the graduates of the Anderson and Florence programs.

15. On October 6 -7, the OEMO hosted the fall meeting of the Southern Agromedicine Consortium with 40 agricultural and medical faculty from seven states attending. As host of the meeting, the OEMO's Agromedicine Program was recognized as a national leader in this sub-speciality of environmental and occupational medicine.

16. On December 15-16, Dr. Simpson met with Dr. Gregory Phelps at the Family Medicine Center/Occupational Health Center of the Medical College of Central Georgia in Macon, Georgia, to discuss strategies for a national meeting on EOM curriculum in family medicine. Dr. Phelps chairs the Occupational and Environmental Medicine Interest Group of the Society of Teachers of Family Medicine.

17. Recorded cases that are described in the January-March Monthly Summary Reports.

    - Copies of reports (164)

18. The EMCC met February 2-3, to critique the first drafts of the nine EOM elective lectures. OEMO staff members revised the drafts in accordance with the committee's suggestions and returned them to the EMCC in mid-March for final review. The nine EOM elective modules are as follows (Modules 1-5 comprise the core EOM curriculum):

Module 6- Carpal Tunnel Syndrome: Diagnosis, Treatment and Prevention

Module 7-	Acute and Chronic Occupational Low Back Pain: A Review for Family Physicians
Module 8-	Noise Induced Hearing Loss in Primary Care
Module 9-	Environmental and Occupational Chemical Exposure
Module 10-	Environmental and Occupational Skin Disease
Module 11-	Environmental and Occupational Lung Exposure
Module 12-	Workplace Substance Abuse: Recognition, Detection and Treatment
Module 13 -	Low Dose Risks
Module 14 -	Title 42: SC Workers Compensation Law: What Should the Family Physician Know?

19. Published the monthly newsletter, *Environmental Medicine Update*, January-March.

    - Copy of newsletter (165)

20. On March 30, Dr. William Simpson led the two-hour workshop, "Environmental and Occupational Medicine in Family Medicine: A Longitudinal Curriculum for Family Medicine Residents," at the Prevention '95: Annual National Preventive Medicine Conference held in New Orleans, LA. The first hour consisted of an overview of designing a three year curriculum for busy family medicine residents, utilizing five core modules and nine elective modules, with input from seven residency training programs. The second hour was a demonstration of one core and one elective module, utilizing slide-lecture and/or interactive self-study, computer-assisted formats.

21. A committee of nursing faculty from the MUSC College of Nursing was appointed to work on a project to adapt the EOM core curriculum to the nurse practitioner program.

22. Dr. William M. Simpson, Jr, attended the Conference of Risk Assessment Issues for Sensitive Human Populations held April 25-27 held at Wright-Patterson Air Force Base, Ohio.

23. The EMCC met May 25-26. The nine elective EOM modules were distributed to the seven family practice residency sites and discussions on the implementation of the core and elective curriculum were held. The nine EOM elective modules are:

Module 1- Carpal Tunnel Syndrome: Diagnosis, Treatment and Prevention

- Copy of module (166)

Module 2- Acute and Chronic Occupational Low Back Pain: A Review for Family Physicians

- Copy of module (167)

Module 3- Noise Induced Hearing Loss

- Copy of module (168)

Module 4- Chemical Exposure

- Copy of module (169)

Module 5- Occupational Skin Disorders

- Copy of module (170)

Module 6- EOM Lung Disease

- Copy of module (171)

Module 7- Workplace Substance Abuse: Recognition, Detection and Treatment

- Copy of module (172)

Module 8- Low Dose Risks: Distinguishing Perceptions from Science

- Copy of module (173)

Module 9- Workers Compensation: What Should the Family Physician Know?

- Copy of module (174)

24. Published the monthly newsletter, Environmental Medicine Update, April-June and produced spring monthly summary reports.

    - Copy of Environmental Medicine Update - Volume 2, Numbers 9-11 (175)

    - Copy of April-June Monthly Summary Reports (176)

25. Completed the initial survey of alumni of the SFPRP. Began a follow-up survey of the Greenwood and Columbia graduates because of poor response to the first mailing.

26. A committee of MUSC nursing faculty was formed in the spring quarter to assess the possibility of adapting the EOM core curriculum to the Family Nurse Practitioner Program. Dr. Barbara Edlund, a member of this committee, met with Dr. Simpson on April 6 to review the materials. The modules were provided to Dr. Edlund for review by her committee. The OEMO is awaiting a decision by the committee as to whether or not the materials can be adapted to the nurse practitioner program.

27. Presented activities of the OEMO and EMCC in a paper delivered by Dr. R. Martin Jones on April 20 at the American Nuclear Society Topical Meeting on Emergency Preparedness and Response in Savannah, GA. Abstract by Schuman S.H., Simpson W.M. and Jones R.M. "Preparing Family Practice Physicians for Environmental Health Incidents and Health Concerns in the Community."

    - Copy of abstract (177)

Milestones and Products Projected for Year 4

1. Will provide continued EOM consultative and research services to the Statewide Family Practice Residency Program (SFPRP) and other health professionals. Will produce monthly summary reports documenting the number and nature of the consultations.

    - Copies of summary reports

2. Will continue to develop of EOM Curriculum for the SFPRP. Will produce Macintosh versions of the elective EOM curriculum computer programs.

    - Copies of diskettes

3. Will update (Version 2.0) of the core EOM curriculum computer programs.

    - Copy of diskettes

4. Will continue to implement the core and elective curriculum at the SFPRP sites. Will document the implementation of a required one month rotation with the OEMO for the third year residents of the MUSC Department of Family Medicine.

    - Copy of reports

5. Will continue to provide EOM lectures by OEMO staff.

6. Will publish the monthly newsletter, *Environmental Medicine Update.*

    - Copies of the newsletters

7. Will produce final report on the survey of SFPRP graduates for the extent of EOM in private practice and for their recommendations for EOM curriculum in residency training.

    - Copy of final report

8. Will make a decision regarding the national dissemination of the EOM core and elective curriculum for family medicine residents. Options include marketing the curriculum modules and/or placing the modules on the World Wide Web.

9. Survey general practitioners in South Carolina to determine the need and desire for EOM continuing medical education.

    - Copy of final report

10. Host the October 25-26, 1995 symposium "The Environmental Risk Assessment: Does it Work for the Community-Based Family Physician?"

    - Copy of white paper

11. Will work with Clemson University engineering faculty to develop risk assessment curriculum for graduate seminars.

12. Will explore the concept of a flexible EOM internship for various disciplines to meet individual needs for EOM and risk assessment.

7.0 Information Support and Access Systems

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Executive Summary

This project supports 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 the first year of the program, core equipment, based on the design architecture was purchased. Installation of this equipment continued through the second year. The major focu during the second year of the c it was to generate preliminary designs of an information access sy: :1 which will serve researchers, health practitioners, and other environmental professionals. To achieve this, we completed extensive surveys of needs and available information sources, and developed the first prototype systems. 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 will be developing data integration techniques to assist the user in identifying and retrieving as much relevant data as is possible from a wide range of sources.

During the third year of the grant, we continued to expand our access to existing databases and incorporate new capabilities into our One Door Access System (ODAS). To broaden ODAS's information access we are working with existing commercial database vendors to develop integrated access methods for their products via the ODAS. We completed the development of an access module that provides ODAS with the capability of accessing Silver Platter databases. Silver Platter, a commercial database vendor, provides over 200 databases to its clients. In addition, two new database access methods were implemented and integrated with the ODAS prototype, ODBC--to access X-based databases (e.g., Paradox, Foxpro, Dbase) and DXP--to access databases provided on CD-ROM by Silver Platter.

In conjunction with the National Library of Medicine (NLM), we have incorporated their Unified Medical Language System (UMLS) products into the ODAS. Specifically, we have integrated both the UMLS Metathesaurus--a database of standard vocabularies and classifications used in the field of biomedicine--to help users narrow or broaden the scope of their searches and

the UMLS Information Sources Map--a database that describes the available electronic information sources in machine-readable form to provide automatic access to those sources.

Year 3 of the project has also seen continued development of our "gopher" server as well as implementation of a World Wide Web (WWW) server. During the third quarter we went on-line with an EHAP WWW server. By year end, we developed a working prototype of the ODAS system that incorporated wider information access capability and benefits from our cooperative efforts. Our collaborators include: the National Library of Medicine and the Micromedix Project with Georgetown University and our in-state alliances with Environmental Medicine Curriculum Committee, Area Health Education Centers (AHEC) Libraries, and the Charleston Academic Libraries Consortium (CALC).

The emphasis for year 4 is to implement ODAS in "real world" settings. We will put a system in the Occupational and Environmental Medicine Office. Then, we will analyze the usefulness of the system. We will iterate changes to the system to improve this "real world" implementation of ODAS.

Dr. Barry Weissglass, an occupational medicine doctor, has expressed an interest in applying ODAS technology in his office. His needs differ slightly from OEMO's, mostly in portability requirements. He travels across the state and wants access to the various systems 24 hours a day from anywhere.

Objectives

1. To build and maintain the basic computer and network structure for information handling.

2. To support the Education Initiative.

3. To support Seminars, Research, and Risk Assessment.

4. To provide operational support of EHAP's overall internal computing and communications.

Milestones and Products for Year 3

1. Developed prototype implementations of the UMLS Metathesaurus and Information Sources Map Modules in association with the ODAS system. NLM's Metathesaurus Module is the central vocabulary of the Unified Medical Language System (UMLS), which is a database of information on concepts that appear in one or more of a number of controlled vocabularies and classifications used in the field of biomedicine. Using the Metathesaurus Module, ODAS users can use a

structured approach to search through large amounts of biomedical data and identify concepts relevant to their ODAS search queries. Like the Metathesaurus, NLM's Information Sources Map Module is an information retrieval tool, which allows users to review detailed information on electronically available information sources. For example, this module will provide information about the provider, content, point-of-contact, number of records, language, etc. of each information source. It can be viewed as a "Yellow Pages" to available biomedical/environmental databases.

- ODAS prototype (178)

2. Completed installation of the CD Plus/Ovid search software on MUSCLS and the Gopher Server. Medline and five other databases are available now across the campus network.

3. Completed a first prototype WWW server in November.

4. MUSC gopher server was enhanced by adding a section addressing the specific needs for Environmental Medicine practitioners.

5. Prototype implementations of the UMLS Metathesaurus and Information Sources Map Modules were further developed in association with the ODAS system. Both have been thoroughly tested and reviewed by EHAP faculty and researchers and by the staff of the National Library of Medicine. (Betsy Humphreys, Deputy Associate Director, Library Operations, Unified Medical Language System Metathesaurus Project; Melvin L. Spann, Ph.D., Chief, Biomedical Information Services Branch; Lawrence C. (Larry) Kingsland III, Ph.D., Assistant Director for Applied Informatics; R.P.C. (Rick) Rodgers, M.D., Department of Health and Human Services, Public Health Service and others. By using the Metathesaurus Module, (the central vocabulary of the Unified Medical Language System (UMLS), ODAS users can use a structured approach to search through large amounts of biomedical data and identify concepts relevant to their ODAS search queries. NLM's Information Sources Map Module is also incorporated into the ODAS as an information retrieval tool, allowing users to review detailed information on electronically available information sources. A further demonstration with a critique was conducted for Georgetown University's Library Information System (LIS) Project team. (Jeff Hylton, LIS Project Manager; Naomi C. Broering, Director, Biomedical Information Resources Center; the Medical Center Librarian and staff)

- ODAS prototype (179)

6. Training continued in access and search strategy to CD Plus/Ovid search software on MUSCLS and the Gopher Server which was installed in the first quarter of year three. Databases include: Full-MEDLINE (back to 1965), CancerLIT, Health Administration, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycInfo, Current Contents including: Life Sciences, Clinical Medicine, Agriculture, Biology and Environmental Sciences, Engineering, Technology and Applied Sciences, and Social and Behavioral Sciences.

7. Demonstrated the first and second prototypes of the ODAS system.

8. Added further enhancements and information to the WWW server to prepare for on-line capability on 2/27/95.

9. The Biomolecular Computing Resource began to support the SAS, IMSL, and PV-Wave software on the SGI research computing network.

10. The MUSC librarians and EHAP staff continued to educate South Carolina family medicine physicians and AHEC librarians and information professionals on the availability of information through telecommunications. Database accessibility was officially announced to and supported by the Charleston Academic Libraries Consortium (CALC) which includes the College of Charleston, The Citadel, Trident Technical College, Fort Johnson, Charleston Southern University and the Charleston County Public Library. Negotiations with the up-state Application Network (AppNet) are currently underway.

11. Refined a first high-level design for a fully functional ODAS system. It includes the development of the hardware and software client/server architecture designs, the Knowledge Base database design, and data flow diagrams (DFDs) that define the high-level system modules and information flows.

    - System design diagrams (180)

12. MUSC's research computing network was linked with the Intel Paragon supercomputer at the University of South Carolina and with similar systems at Oak Ridge and Sandia National Laboratories. The first in a series of planned tutorials was held in November for MUSC faculty and graduate students on the Intel Paragon.

13. Established a "technical partnership" agreement with SilverPlatter, a commercial database vendor. Under this agreement, the ODAS Development Team received SilverPlatter's Application Program Interface (API), allowing software to be developed to access SilverPlatter databases via the ODAS. The SilverPlatter client software

was successfully modified to compile on the SGI platform, and significant progress was achieved toward establishing access to SilverPlatter databases. In fact, the DXP (Data Exchang Protocol) interface for ODAS was completed and integrated with the ODAS prototype.

14. Completed the interface for PC type databases. This new interface allows ODAS to interrogate X-based databases, (Foxpro, Paradox, Dbase), using Microsoft's Open Database Connectivity product.

15. Held the first Information Systems Review February 27-28. The review panel included: Sherrilynn S. Fuller, Health Sciences Library and Information Center, University of Washington; John L. Shnase, Director, Advanced Technology Group, Biomedical Communications Center, Washington University School of Medicine; and Karen T. Hackleman-Dahlen, Associate Professor and Head of Information Services, The University of Illinois. The group reviewed all aspects of the Information System portion of the grant and will make recommendations as to how the program might proceed to better meet the objectives. They reviewed both the objectives of the program and the methods being used to achieve them. We expect their report by the end of April.

16. Implemented and brought on-line the EHAP WWW server. Completed internal report on progress and projections for development of the Web.

    - Copy of report (181)

17. Completed design of the Research Computing Network and installed new SGI machines in biometry to facilitate research there.

18. Implemented development of two data access methods and integrated these with the ODAS prototype. The first method uses Microsoft's Open Database Connectivity (ODBC) product to access X-based databases (e.g., Paradox, Foxpro, Dbase, Access) residing on PCs. The second access method uses the Data Exchange Protocol (DXP) to access databases provided on CD-ROM by Silver Platter. The ODAS now provides the capability to access relational databases, X-based databases, and Silver Platter databases simultaneously, via a single user interface.

19. Initiated development of a PC-based ODAS client application. The current ODAS client executes on Silicon Graphics hardware. A PC-based client will make the ODAS more accessible to the target user community (e.g., rural physicians, researchers, academicians, clinicians).

20. Continued development of the capability to access Z39.50-compliant databases via the ODAS. This capability will greatly increase the number of databases available through the system. We have successfully ported the Stanford University Z39.50 client software to the Silicon Graphics machine.

21. Began design of an ODAS-based system for the MUSC Occupational and Environmental Medicine Office (OEMO) as an initial "beta-site" system. We worked with OEMO to understand their unique information access requirements.

22. Began the design of a distributed processing architecture for ODAS. The purpose of this initiative is to migrate the ODAS to a distributed client-server architecture in order to increase data access time. In addition, this architecture will be entirely PC-based, which will make it a viable information access solution for a larger user community.

23. Continued to coordinate our efforts with related research efforts throughout the U.S.

Milestones and Products Projected for Year 4

1. Will establish a complete working ODAS at MUSC, whereas previously the versions in Charleston have been demonstration systems only.

2. Will implement ODAS with MUSC's Occupational and Environmental Medicine Office.

3. Will iterate solutions of ODAS with OEMO.

4. Will start working with Dr. Barry Weissglass (an occupational medicine physicians) and also modify the ODAS at MUSC to his needs.

5. Will investigate remote access methods to ODAS.

6. Will demonstrate a connection between a Z39.50 client and a Z39.50 database.

7. Will demonstrate the initial version of the PC Client application.

8. Will continue to develop EHAP's World Wide Web (WWW) page, integrating more graphics and latest enhancements of HTML.

9. Will support the Crossroads database with new enhancements including report generation.

10. Will continue to demonstrate Information Systems (ODAS, WWW, and Crossroads).