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DOE/EW/50625--724

ENVIRONMENTAL HAZARDS ASSESSMENT PROGRAM QUARTERLY REPORT

April--June 1995

FOR

GRANT DE-FG01-92EW50625

SUBMITTED TO THE
U.S. DEPARTMENT OF ENERGY

BY THE

MEDICAL UNIVERSITY OF SOUTH CAROLINA

July 31, 1995

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Quarterly 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. 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.
- 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.
- 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.
- 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's 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 a comprehensive, long-term plan for the Charleston Enterprise Community (EC). Called the Healthy Community Initiative, this plan 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 TCE Data Analysis Project peer review from March 23-24 in Charleston. To follow-up 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 fourth quarter (April-June) of 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) 792-1616.

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 continue 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 continues 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. The Science element continues work on numerous research projects, concentrating on trichloroethylene-related assessments, 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 expenditures for the Fourth Quarter and year-to-date Year 3 grant expenditures.

<u>EHAP 4th Quarter Year 3 Expenditure Summary</u>	<u>4th Qtr</u>	<u>YTD</u>
	(Dollars in thousands)	
Public and Professional Outreach	\$455	\$1,213
Crossroads of Humanity Series		
Publications/Information		
Research and Evaluation		
Professional Training		
Science Programs	766	2,007
Toxicology		
Risk Assessment		
Education		
Clinical Programs	150	484
Health Services Research		
Family Medicine		
Information Systems	654	1,288
Indirect Costs	725	1,962
Equipment	108	198
Total	\$2,858	\$7,152

MUSC has until August 1995, to settle on all outstanding encumbrances and commitments for the grant year. At that time a final invoice will be submitted. All obligated funds will be expended in support of the program for Year 03.

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 Management 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 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 Fourth Quarter, Year 3

1. 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. Dr. Mohr's 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.

2. In collaboration with Coleman Research Corporation (CRC) and the Atomic Energy Authority Technology Consultancy Services (AEA) of the United Kingdom, we initiated the "Risk Assessment/Risk Management International Symposium Study." Through June 30, 1995, the following project activities had taken place: Kickoff Meeting (5/3/95, Washington, DC) and first Steering Committee Meeting (6/15-16/95, Charleston, SC). At the Steering Committee meeting, representatives of AEA Technology presented a summary of risk assessment/risk management practices in Europe compared to those in the United States, then suggested topics for illustrative case studies. The Steering Committee also discussed dates and formats of future meetings and presenters and audience for those meetings.
3. We continued to revise the second draft of a program review of EHAP, projecting the activities of each project throughout the life of the grant.
4. We held strategic planning sessions to seek options and to find answers dealing with what EHAP will do when the original grant funding expires.
5. On May 31, Dr. David Jollow and Dr. David G. Hoel received the final copy of ChemRisk's report, which was first presented at the TCE Data Analysis Project peer review from March 23-24 in Charleston.
 - Copy of the report
6. We continued final editing of manuscript on the survey of dental educators regarding environmental issues in dental training, which will be submitted to the Journal of Dental Education. This work is a collaborative effort of MUSC College of Dental Medicine (W. Burton and R. Draughn) and the professional staff of EHAP (C. Musham).
7. We established a small library at 156 Rutledge Avenue, which allows EHAP staff easy access to Program-generated documents as well as those books purchased during the life of the grant. Also, we created a hard copy and computer version of a library index for these collected publications.

Milestones and Products Projected for First Quarter, Year 4

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

2. Will complete manuscript on the survey of dental educators regarding environmental issues in dental training and will submit it to the Journal of Dental Education. This work is a collaborative effort of MUSC College of Dental Medicine (W. Burton and R. Draughn) and the professional staff of EHAP (C. Musham).
 - Copy of manuscript
3. Will develop programs to define collaborative efforts between EHAP and academic research and teaching programs in South Carolina.
4. In collaboration with Coleman Research Corporation (CRC) and the Atomic Energy Authority Technology Consultancy Services (AEA) of the United Kingdom, we will continue help to coordinate the "Risk Assessment/Risk Management International Symposium Study." The Steering Committee will hold its next meeting in Charleston, SC, July 25-26.
5. 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.
6. 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.

4.0 PUBLIC AND PROFESSIONAL OUTREACH

4.1 Crossroads

Executive Summary

During the fourth quarter of year three, Public and Professional Outreach built upon the work and planning of preceding quarters 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.

In the areas of Research and Evaluation, the Crossroads staff continued a public-participation project in the rural-agrarian community of Blackville, SC. The Blackville Project is designed to measure citizens' perceptions of environmental risks to human health in their community, then supplement citizens' knowledge via coordinated, multi-media outreach efforts. We will apply lessons learned from the Blackville Project in partnerships with other communities:

One such "community" is the so-called "Neck" area of Charleston. During the third quarter, the U.S. Department of Housing and Urban Development (HUD) designated portions of the Neck and contiguous areas as an Enterprise Community (EC). During the fourth quarter, EHAP staff interfaced with federal, state and local officials to develop a partnership approach to the EC designation. MUSC/EHAP will serve as a primary partner in development and implementation of a "Healthy Community Initiative," designed to improve the overall environmental health of the Charleston EC.

One portion of the Healthy Community Initiative may be development of a business relationship with industries in the Charleston EC. During the fourth quarter, Crossroads staff met with representatives of Albright & Wilson of the Americas, a chemical-manufacturing company situated in the Charleston Neck area. The result of these meetings may be a multi-disciplinary review and outreach effort, funded by Albright & Wilson and performed in large part by MUSC/EHAP.

Crossroads staff continued publication and information efforts in support of MUSC/EHAP. These include: the quarterly EHAP newsletter; ongoing redesign 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 Blackville, SC, and the Charleston "Neck" area.
3. To publish printed materials related to EHAP and the Crossroads Series.
4. To publish material and provide information support of Program Management, Science, Education and Information Systems initiatives.
5. 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 Fourth Quarter, Year 3

1. Continued Phase II of Blackville Project described in above introductory overview segment of Crossroads Series quarterly report.
2. Conducted essay contest for students in grades 3-12. More than 200 essays were submitted. Prizes were awarded to the top three essays in the elementary, middle and high schools.
 - Copies of essays
3. Co-sponsored Barnwell County Chamber of Commerce Business After hours on April 25. More than 100 people attended.
4. Established Blackville database containing nearly 1,000 households within Blackville.
5. Continued ongoing series of planning meetings with MUSC/Blackville liaison Ms. Mildred Ford and MUSC/EHAP staff Mrs. Sylvia Rivers, Ms. Amy Hovatter and Ms. Cathi Bare.
6. Conducted and/or attended meetings related to development of a partnership between federal, state and local officials and MUSC/EHAP

for the purpose of inaugurating a Healthy Community Initiative in the Charleston Enterprise Community (EC).

7. Continued ongoing series of meetings between Mr. David 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.
8. Attended meeting on June 5 at Charleston (SC) City Hall for purpose of discussing the Medical University's role as a major partner in application of a Healthy Community Initiative in the Charleston EC. Those in attendance included: Mayor Joseph P. Riley, Jr. and Ms. Patricia Crawford of the City of Charleston; U.S. Congressman James Clyburn and Mr. Davis Marshall from his staff; and Dr. Lawrence C. Mohr, Jr., Mr. David Rivers and Mr. Richard Jablonski from MUSC/EHAP.
9. 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.
10. Conducted meeting on June 22 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. Lawrence Mohr, Dr. Glenn Fleming, Ms. Susan Legare and Mr. Richard Jablonski of MUSC/EHAP.
11. Attended follow-up meeting on June 26 at Albright & Wilson plant. Meeting attended by Mr. Bill Helfenstein, Mr. John Stoney and Mr. Moses Clarkson of Albright & Wilson, and Mr. Richard Jablonski of MUSC/EHAP.
12. Continued to overhaul the Crossroads of Humanity database, adding experts as they were identified. This effort continues each quarter so as to provide user-friendly access to the data critical for networking. Database currently contains 3,506 entries.

13. 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 First Quarter, Year 4

1. Will continue Phase II of the Blackville Project.
2. As part of MUSC/EHAP's leading partnership role, will work toward 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.
3. Will enter partnership with Albright & Wilson of the Americas 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 Fourth Quarter, Year 3

Research Activities

1. Completed revisions of dental educator survey designed to assess dental educators' perceptions regarding the need for environmental health education in graduate school.
2. 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)
3. 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
 - Survey Instrument
 4. Completed preliminary planning phase for testing the feasibility of using Crossroads "Purity" Roundtable videotapes as educational tools.
 - Phase one documentation
5. Received 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).

Dissemination of Research Results

6. 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.
 - Finished manuscript
7. Dr. Catherine Musham presented the results of the paper "Environmental Preparedness: Helping Communities Plan for Environmental Incidents" at American Nuclear Society's Fifth Topical Meeting on Emergency Preparedness and Response in April.
 - Manuscript
8. Submitted two abstracts for the Annual Association of Public Health Convention in San Diego in November 1995. Both were accepted.
 - Copies of abstracts
9. Submitted two abstracts for the annual Society of Risk Analysis Conference in December 1995.
 - Copies of abstracts

Professional Networking

10. Attended monthly South Carolina Family Practice Research Consortium meetings for continued support of environmental risk perception and communication research.
11. Continued coordination efforts with Dr. John Eureka of the University of South Carolina in establishing a South Carolina Risk Perception and Communication Computer Network.
12. Dr. Catherine Musham met twice with Dr. Abe Wandersman and Dr. Cathy Wilson, director of Family Institute in Columbia, to discuss their involvement in the Enterprise Community Program.
13. 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.
14. Dylan Holmes met with Dr. Abe Wandersman to explore research possibilities of psychologists into environmental health.

Education and Reference

15. Met with Dr. Jan Temple to review and add input to a risk communication training program. Dr. Catherine Musham prepared and presented a segment on Risk Perception Research.

Milestones and Products Projected for First Quarter, 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 draft of 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 Fourth Quarter, Year 3

1. Published and mailed spring newsletter.
 - EHAP News & Information
2. Planned publication of August 1995 EHAP newsletter.
3. Published/distributed announcement of Dr. Lawrence Mohr's appointment as director of MUSC/EHAP.

4. Continued development and implementation of 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>
5. Published/distributed EHAP Fact Sheets on development of an MUSC/EHAP "home page" on the World Wide Web.
 - Fact sheets
6. 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.
7. Continued design process for a new generation of MUSC/EHAP brochures and information sheets.
8. Planned publication and logistical support for second meeting of EHAP External Advisory Group, scheduled July 24-25, in Charleston.
9. Planned publication and logistical support for second meeting of International Risk Assessment/Risk Management Forum Steering Committee, scheduled July 25-26, in Charleston.
10. Continued in-house newspaper, magazine and publication "clip file."
11. Submitted news releases to MUSC's weekly newspaper, *The Catalyst*. Four stories were published.
 - Copies of stories
12. Initiated presentations at MUSC's library about EHAP-sponsored programs.

Milestones and Products Projected for First Quarter, Year 4

1. Will publish and mail summer EHAP News & Information newsletter.
2. Will plan publication of fall and winter 1995 EHAP newsletters.
3. Will continue development and implementation of MUSC/EHAP "home page" on the World Wide Web.
4. Will continue 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.

5. Will continue design process for a new generation of MUSC/EHAP brochures and information sheets.
6. Will provide publication and logistical support for second meeting of EHAP External Advisory Group July 24-25.
7. Will provide publication and logistical support for second meeting of International Risk Assessment/Risk Management Forum Steering Committee July 25-26.
8. 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 task is to address workforce management training needs in a rapidly changing environment. One of the environmental industry's missions is to ensure that resources are available to assure the current and future workforce has the skills, knowledge and abilities to carry out its mission today and in the future. 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 executives, managers and workers who will be involved with environmental cleanup and restoration issues within government, business, and industry.

The Department of Environmental Health Sciences is involved in the outreach initiative with a focus on education and training. A Risk Management Advisory Committee has been established to render guidance to this task. It includes representatives from EPA, OSHA, DOE, DOD, labor unions, educators, public interest groups and the health-care community. The fifth meeting of the Risk Management Advisory Committee was held June 1-2 in Charleston, SC.

Two new Professional Development seminars were designed and developed during Year 3. The programs vary in length and include: 1) "Risk Communication" - an introduction to risk communication concepts, methods and practice; and 2) Executive Overview of Risk Analysis , which is a course designed to increase awareness and understanding of the risk analysis process and recognize management commitment and support necessary to implement a responsible and responsive corporate policy.

The first course, "Risk Communication," was pilot tested to the Risk Management Advisory Committee in November 1994. The course was well received and beneficial comments were provided by the Risk Management Advisory Committee members. A second pilot was conducted in March 1995 and a final review occurred during the Risk Management Advisory Committee meeting in May. The second course "An Executive Overview of Risk Analysis" was presented to the Risk Management Advisory Committee at their May Meeting.

Two customized risk programs were developed and offered this year to include training of sixty engineers at the Charleston Naval Shipyard.

Milestones and Products for Fourth Quarter, Year 3

Planning/Administration/Networking

1. Continued networking to examine risk related training needs of government and industry facilities.
2. Continued to consider an industry partnership.
3. Began to discuss feasibility of an Idaho National Engineering Laboratory Risk Training program.
4. Initiated a discussion with Governor Beasley's office to incorporate Risk Education and Training into math and science reforms for South Carolina.
5. Continued to maintain an off-site library to house environmental risk assessment, management, and communication information.

Risk Management Advisory Committee

6. 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 stakeholders. 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. Committee members provided comments and recommendations to improve the course content, presentation, and materials through written and verbal evaluations. Responses were highly affirmative. Other recommendations included demonstration of courses and application of risk perception research into the "Risk Communication" course.

- List of committee members
- Copy of meeting agenda

Risk Program Design and Development

7. Continued course development for the second Professional Development Seminar, "Decision Making in Environmental Risk Management," which now has 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
8. 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
9. 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

Research/Publications/Presentations

10. 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.

11. Submitted abstract to Society for Risk Analysis.

- Copy of abstract

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

Outreach/Speaking Engagements

13. 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.
14. Presented "Lead Health Risks" at premier presentation of Charleston Childhood Lead Poisoning Prevention video.
15. Addressed the Charleston County Health Department as a guest speaker regarding the future of Environmental Health.

16. 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 SC when health issues surfaced.

Milestones and Products Projected for First Quarter, Year 4

Planning/Administration/Networking

1. Will continue to network and meet with a wide range of colleagues and potential partners and clients.
2. Will continue to investigate collaboration with private sector to commercialize risk courses.

3. Will continue to work with the Citizen Advisory Boards at hazardous waste sites across the nation.
4. Will explore venues with University Medical Associates.
5. Will continue to interact with State of South Carolina initiative for math and science K-16 to include risk education and training.

Risk Management Advisory Committee

6. Will conduct a final review of the fourth Professional Development Seminar, "Executive Overview of Risk Assessment."

Program Design and Development

7. Will pilot test and finalize "Executive Overview of Risk Analysis."
8. Will develop a risk perception research module.
9. Will confirm demonstration sites for professional enhancement series course(s) and begin design of follow-up instrument.
10. Will refine risk leadership initiative.

Research/Publications/Presentations

11. Will submit abstracts to the National Association of Environmental Professionals and the Environmental Information Association.
12. Will continue the risk survey in schools.

Outreach

13. Will continue to be involved in Charleston's "Neck" area Enterprise Community initiative.
14. Will serve on conference planning committee for National Association of Environmental Professionals (NAEP) with responsibility to review abstracts in risk analysis for the 1996 annual conference scheduled June 1-6, 1996 in Houston.

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

The above project was not funded for the previous quarter. It is noted above for reference because it will be included in the annual report for Year 3.

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 which 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 Fourth Quarter, Year 3

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

Milestones and Produces Projected for First Quarter, 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, led by Dr. Pandey.

The Assessment of Genetic Risk to Environmental Diseases project is pursuing funding from other sources.
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5.1.3 <u>Identification of Trichloroethylene-Hemoglobin Adducts for Use in the Development of an Immunological Assay to Assess Trichloroethylene Exposure in Humans</u>
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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.

During this fourth quarter, we have completed work 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.

As was detailed in the third quarter report, the first inhibitor prepared for determination of antibody specificity, N^ε-dichloroacetyl lysine, was synthesized by reacting lysine with dichloroethiolacetate. The second inhibitor, N^ε-trichloroacetyl lysine, was synthesized in a similar manner (i.e., using trichloroethiolacetate), and was collected and purified by recrystallization from ethanol. However, synthesis of the third inhibitor, N^ε-monochloroacetyl lysine, proved more difficult. In the process of reacting mono-chloroethiolacetate with L-lysine, a by-product was formed that was later identified by mass spectrometry and NMR spectroscopy as a thioether derivative of N^ε-acetyl lysine. This by-product was similar chemically to the monochloroacetyl lysine inhibitor product, which made purification of the product by conventional methods quite difficult. Thus, the mono-chloroacetyl lysine had to be purified chromatographically using semi-preparative high performance liquid chromatography.

Upon completion of the synthesis, the inhibitors were sent to Dr. Neil Pumford, collaborator for this project, at the University of Arkansas for Medical Sciences, in Little Rock, AR. The inhibitors were used in two ways. First, the inhibitors were used in a competitive ELISA (enzyme-linked immunosorbent assay) format to determine what chemical structures the antibody could recognize. Second, the inhibitors were used in a Western blot format to determine if, and how well, they could inhibit binding of the antibody to TCE adducts on liver proteins from mice treated with TCE. The results of these studies indicate that the antibody recognizes dichloroacetylated protein adducts with a high degree of specificity. The antibody also recognizes mono- and trichloroacetylated adducts, but to a much lesser extent. The dichloroacetyl lysine inhibitor was also able to displace completely antibody binding in the Western blot experiment. The data also indicates that antibody sensitivity for adduct detection is in the picomolar (10^{-12} M) range. This data shows that we have a highly specific anti-TCE antibody that can recognize TCE-protein adduct formation *in vivo*.

The data from this work is being prepared for submission to *Chemical Research in Toxicology*, a draft of which will appear in the 1994-95 Annual Report. Other faculty who worked on the project include Dr. John Oatis,

Assistant Professor of Pharmacology at MUSC and Dr. Herbert Ashline, Professor of Chemistry at Claflin College.

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 Fourth Quarter, Year 3

1. Completed the synthesis of anti-TCE antibody inhibitors. Generated data were in the form of HPLC chromatograms, and mass and NMR spectra.
2. Completed characterization of antibody specificity/sensitivity using the inhibitors described above in a competitive ELISA format.
3. Submitted a manuscript on the above studies to the journal *Chemical Research in Toxicology*.

Milestones and Products Projected for First Quarter, Year 4

1. Will purify TCE-adducted proteins from mice treated with TCE using immunoaffinity chromatography.
2. Will develop experimental procedures to enzymatically digest purified proteins to amino acids, develop chromatographic methods to isolate amino acids from digested proteins for structural analysis.
3. Will continue identification of amino acid adducts recognized by the anti-TCE antibody in mice.
4. Will examine whether human serum samples from scleroderma patients (obtained from Dr. Richard Silver) have antibodies that recognized TCE-protein adducts.

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 B6C3F₁ 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 B6C3F₁ 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 Fourth Quarter, Year 3

1. In continuation from the previous quarter, 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
 - Data on TCA induction of DNA synthesis in rat hepatocytes and Hep3B cells
2. 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
3. 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.
4. 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).
5. 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 of Ohio State University to observe isolation of human hepatocytes.
 - Copy of letter outlining arrangements

Milestones and Products Projected for First Quarter, Year 4

1. Will examine the ability of DCA to induce peroxisome proliferation (using both enzymatic and molecular markers) and enhance DNA synthesis in both B6C3F1 mouse and rat hepatocyte cultures.
2. Will compare responsiveness of HepG2 and Hep3B human hepatoma cell lines, with respect to DCA induction of peroxisomes, to the response observed in mouse and rat hepatocyte cultures.
3. Will compare the ability of DCA to induce peroxisome proliferation (using both enzymatic and molecular markers) with that of clofibrate and TCA.
4. Will attend the International Congress of Toxicology VII Meeting in Seattle, WA, on July 2-5 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 O₂-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 O₂-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 O₂-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 (O₂⁻), the hydroxyl (HO·), peroxy (ROO·), alkoxy (RO·), and perhydroxyl (HOO·) radicals, hydrogen peroxide (H₂O₂), 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 Fourth Quarter, Year 3

1. Initiated preparation of a manuscript describing the reaction of HO· with polyunsaturated lipids.
2. Completed a manuscript describing the reaction of HOO· with the deoxyribose-phosphate backbone of DNA.
3. Initiated product studies for the reaction of HO· with the DNA bases.
4. Initiated product studies for the reaction of ROO· with the DNA bases.

Milestones and Products Projected for First Quarter, 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

The research of the laboratory is focused 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.

PCBs

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.

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 PCBs are more easily attacked under anaerobic conditions; and, 3)

some of the more heavily chlorinated PCBs are considered to be more toxic. 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.

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.

Gasoline Additives (MTBE and ETBE)

These compounds are resistant to degradation and can accumulate in groundwater following a gasoline spill. Some gasolines are now 15 percent MTBE. The health hazard that this may pose is not clear and is being debated. Identification and characterization of microorganisms that can degrade these compounds would be very useful in the remediation of a spill site. Thus far, six aerobic strains that degrade ETBE have been isolated in this laboratory. The degradation products have not yet been determined because of delays in the renovation of the lab. Now that we are equipped analysis of these and future strains can proceed.

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, during the long-term, 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, during the long-term, bioremediation of ground waters contaminated with the aforementioned ethers.

Milestones and Products for Fourth Quarter, Year 3

Research

1. Perhaps the most important milestone is that the laboratory renovation was completed at the end of May. Equipment for the analysis of PCBs and ethers has now been installed and an anaerobic chamber for the cultivation of anaerobic microorganisms is being installed.

Project A: Anaerobic Dechlorination of Polychlorinated Biphenyls

2. The marine and estuarine enrichments, described in the third quarter report, continue to express the rare dechlorination of *ortho* chlorines on the biphenyl rings. The initial characterization of this activity will be presented at a Gordon Conference on Applied and Environmental Microbiology next quarter.
3. 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

4. An organism has been 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

5. A summer undergraduate student, Aliyah Spruill, has 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 First Quarter, Year 4

1. Will submit for publication a manuscript describing the *ortho* PCB dechlorination observed with Baltimore Harbor sediment.
2. Will submit for publication a manuscript describing the isolation of DNA from sediments heavily contaminated with coal-based humic acids.
3. Will determine the ability of Baltimore Harbor sediments to dechlorinate Aroclor 1242 (commercial mix of PCBs).
4. Will determine degradation products of ETBE-degrading isolates.

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 Fourth Quarter, Year 3

1. 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.
2. 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)
3. 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.
4. 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.
5. Dr. Lucille London of MUSC's Department of Microbiology and Immunology 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.
6. Three Ph.D. students (Samuel Rawlin, Romish Stanislaus, and Roberto Frontera-Suau) have been conducting their dissertation research in the laboratory.

Milestones and Products Projected for First Quarter, 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.

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 M. 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 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 Fourth Quarter, Year 3

1. Constructed the fos-luciferase (fos-luc) reporters. We are now testing their functionality by transient expression approaches following stimulation with phorbol esters (control) and TCE metabolites (test).
2. Continued testing fos-luc vectors in Dr. Frawley's photon counting apparatus under conditions (established above) where vector expression is observed.
3. Continued to establish conditions for photon counting that will later be analyzed for suitability in the comet assay.
4. Continued 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.

Milestones and Products Projected for First Quarter, Year 4

1. Will expand the program to include all of the above milestones for fourth quarter. We will continue unabated and will add several experiments noted below.

2. Will develop functional knockout vectors for the following peroxisomal enzymes: catalase, Acyl-CoA oxidase and Acyl-CoA synthetase. We will also develop vectors (to be decided) to perturb the PPAR system. These functional knockout vectors are based on the triple ribozyme * vector that Drs. Norris and Clawson (Penn State) are developing. These vectors are designed to determine the role of peroxisomes in TCE-induced hepatocellular carcinoma in B6 mice.

* This vector (patent applied for) is based upon a ribozyme construct targeted to inactivate the gene of interest flanked by two autocatalytic ribozymes that cleave to produce a short RNA molecule available to act in the nuclear environment.

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, TNF α , IL-1 α 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. TNF α , IL-1 α and β are important in several immunological activities and are mediators of inflammatory responses. TNF α 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 percent 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, TNF α , 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 Fourth Quarter, Year 3

1. 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. Consulted with Dr. Mustafa Dosemeci, from the Environmental Epidemiology Branch at the National Cancer Institute, consulted April 12 -13. He provided us with an overall critique of the project proposal and 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.
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

Milestones and Products Projected for First Quarter, Year 4

1. Will continue to research the association of scleroderma with occupational and environmental exposures and characterize 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 P450III β 1 gene.

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.
4. To understand through basic biological models the effects of radiation induction of misrepaired double strand breaks at the cellular level.

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 Fourth Quarter, Year 3

1. 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
2. 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 model considerations. Completed draft report.
 - Copy of report

3. 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
4. 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 First Quarter, Year 4

1. Will begin work at the laboratory of Dr. R. H. Schiestl of the Harvard School of Public Health. The purpose is to generate needed experimental data for the double strand break and misrepair model. Expect some evaluation of the type of data that can be developed for the model by the end of the quarter.
2. Will compare the modeled dose-response data for rodent tumors in order to estimate dose-rate and relative biological effectiveness factors (RBE). This will provide the basic data for a subsequent manuscript.
3. The PC/windows based PBPK modeling software will have an option to generate system description to be passed to the Intel Paragon super computer at USC-Columbia. We are currently developing the simulation software on the Paragon supercomputer. When this is finished, the end-user can define large scale PBPK model and receive the simulation result in a short time. This can greatly facilitate the model development for problem such as TCE Dose Response Analysis.
4. Dr. David G. Hoel will continue to act as project director for the International Risk Assessment/Risk Management Forum.

5.2.2 Environmental Risk Perception in Defined Populations

Project Leaders:

Daniel T. Lackland, Ph.D.
John B. 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 Fourth Quarter, Year 3

1. 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.

2. 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.
3. 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.
4. Wrote technical report on geographic variation in risk perception.
 - Copy of report
5. Produced a technical report on racial variation in risk perception.
 - Copy of report

Milestones and Products Projected for First Quarter, Year 4

1. Will write preliminary report on analyses from population survey.
2. Will write manuscript on risk perception and geographic variation.

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 B. Dunbar, Dr. P.H. David G. Hoel, Ph.D.
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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 that 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 Fourth Quarter, Year 3

1. 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
2. Presented geo-coding methodology at the Institute of Health in Munich, Germany.
3. Discussed geo-coding methodology with representatives at the Agency for Toxic Substances and Disease Registry.
4. The Office of Research and Statistics continues significant progress at address matching.
 - Copy of report

Milestones and Products Projected for First Quarter, Year 4

1. Will continue geo-coding assessment of Charleston's "Neck" demonstrating capability.
 - Copy of maps
2. Will continue address matching.
 - Copy of progress report

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 TCE. This work will begin with a follow-up of the results of the physiologically based pharmacokinetic (PBPK) modeling 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 Trichloroethylene (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 analysis 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 First Quarter, Year 4

1. We will initiate review of PBPK work of ChemRisk Panel.
2. We 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

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 Fourth Quarter, Year 3

1. Filled teaching position in Risk Assessment. An offer was extended to Dr. Nicholas Lawryk on April 22.
2. 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
3. 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
- 4. A new course, Environmental Epidemiology, is being taught this summer. The course has nine students enrolled.
 - List of students enrolled in course and course announcement
- 5. Developed new course, Environmental Immunology, which will begin in the fall. The instructors are Dr. Karen Burnett and Dr. Robert Galbraith.
 - Course announcement
- 6. Developed Case Studies Course and submitted to the Curriculum Committee for approval.
 - Course description submitted for approval
- 7. Enrolled three students in summer internships.

Milestones and Products Projected for First Quarter, Year 4

1. Continue recruitment efforts for MES students.
2. Finalize drafts for multidisciplinary core courses.
3. Offer continuing Seminar Series in Environmental Studies.

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 in 1995 were in three major areas: environmental health policy, environmental health education and international environmental issues. Research efforts will also focus on social and economic considerations in environmental decision-making, as well as citizen participation issues. A major thrust of the Policy Studies Journal

symposium, the hazardous waste study, and future planned projects is the relation of social and economic issues to environmental policy.

Another major focus of current research is on policies for the management of hazardous waste. Recently a study on perceptions of hazardous waste operators and inspectors was completed. A paper and presentation on comparative views of hazardous waste site operators and inspectors was presented at the June meeting of the National Association of Environmental Professionals in Washington, DC. 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 Fourth Quarter, Year 3

1. 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 article
2. Attended and presented abstract to National Association of Environmental Professionals in June.
 - Paper and abstract noted in conference proceedings
3. Continued preliminary data analysis for two abstracts submitted for presentation at the October 1995 American Public Health Association Meeting in San Diego. Abstracts accepted were: 1) Environmental Clusters and Ranking of Selected Nations; and, 2) An Organizational Typology of Environmental Agencies and Businesses.
 - Copy of abstracts

Milestones and Products Projected for First Quarter, Year 4

1. Will complete data analysis for two abstracts submitted for poster presentation at the October 1995 American Public Health Association

Meeting in San Diego. Will prepare and print posters for presentation at APHA conference.

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 met 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 with many being 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 Fourth Quarter, Year 3

1. 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 First Quarter, 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 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
Administrative Assistant:	Kay Sims

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 SFPRP with consultations on patients with EOM complaints. The work of the committee and EOM consultative resource are ongoing. Future activities include adapting the core and elective EOM curriculum to other disciplines and into self-study programs for the busy practitioner.

Sub-committees of the EMCC worked closely with OEMO staff in the development of the EOM elective EOM curriculum modules. The modules were delivered to the committee on May 26. Project staff consulted on 99 EOM cases during the period and presented five EOM lectures.

In cooperation with Dr. W. Allen Smith, project staff continued to develop plans for a meeting of national leaders in family medicine to discuss the environmental risk assessment process. This will be held in October 1995 in Charleston, SC and will be sponsored by EHAP and the MUSC Department of Family Medicine.

Objectives

1. Provide continued support to the EMCC including EOM consultative and research services to the SFPRP.
2. Develop nine environmental medicine elective curriculum modules for family medicine residents and update core curriculum modules.
3. Determine if the core EOM curriculum can be adapted to other disciplines.

Milestones and Products for Fourth Quarter, Year 3

EOM Consultative and Research Services

1. Continued monthly environmental/occupational medicine literature review for pertinent articles to be added to the project's computerized database.

2. Consulted on 99 environmental/occupational medicine cases.
 - Cases described in April-June Monthly Summary Reports
3. 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.

EOM Curriculum for Family Medicine

4. 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

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

- Copy of module

Module 3- Noise Induced Hearing Loss

- Copy of module

Module 4- Chemical Exposure

- Copy of module

Module 5- Occupational Skin Disorders

- Copy of module

Module 6- EOM Lung Disease

- Copy of module

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

- Copy of module

Module 8- Low Dose Risks: Distinguishing Perceptions from Science

- Copy of module

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

- Copy of module

5. Published the monthly newsletter, Environmental Medicine Update, April-June. The objectives of the newsletter are to report on the activities of the EMCC and to stimulate committee members concerning recent developments in EOM.
 - Copy of Environmental Medicine Update - Volume 2, Numbers 9-11
6. Presented five EOM lectures. Lectures are described in the April-June Monthly Summary Reports.
 - Copy of reports
7. 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. The deadline for the follow-up was set for June 30, therefore, the final report on this activity will be delayed until the next quarter.

EOM Curriculum for Other Disciplines

8. A committee of MUSC nursing faculty was formed last 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.
9. 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

Milestones and Products Projected for First Quarter, Year 4

1. Will provide continued support to the EMCC including EOM consultative and research services to the SFPRP.
2. Will complete final report on the EOM survey of alumni of the SFPRP.
3. Will implement a required one month OEMO rotation for the third year residents of the MUSC Department of Family Medicine.
4. Will develop plans for updating the five core EOM modules.
5. Will continue planning for the October 25-26, 1995 symposium, "The Environmental Risk Assessment: Does it Work for the Community-Based Family Physician?"

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 focus during the second year of the grant was to generate preliminary designs of an information access system 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 expanded our access to existing databases and incorporated 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 provide 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.

During the fourth quarter we have demonstrated the prototype to people from the DOE, Waste Policy Institute, Silver Platter, and the Ames Laboratory. Based on our working ODAS prototype we have shown that a single system can be built which can access a large number of commercial and proprietary databases based on a single query. This is the first system we know of

providing such broad capability. Next, we are moving to build an ODAS based system that will support MUSC's Occupational and Environmental Medicine Office. This will be the first implementation that will result in a "real" product. This system will be built based on the needs of MUSC physicians and should be applicable to the needs of physicians in these specialties across the country. We will continue to coordinate our development efforts with the National Library of Medicine - working with their Unified Medical Language System (UMLS) products into the ODAS.

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 fourth quarter we have expanded the functionality of our WWW server, modifications and upgrades will continue into next year.

There are four main thrusts of the Information Support Project:

- build and maintain the basic computer and network structure for information handling;
- support of the Education Initiative;
- support of the Seminars, Science, and Risk Assessment; and
- support of the Clinical Initiative.

There is one operational responsibility:

- operational support of EHAP overall internal computing and communications

Milestones and Products for Fourth Quarter, Year 3

1. 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.
2. Continued development of the EHAP World Wide Web (WWW) home pages by connecting to other DOE sites, allowing interactive requests and forms and setting up e-mail connections. Completed internal report on progress and projections for development of the Web.
 - Copy of report
3. Broadcasted the EHAP WWW home pages to other health centers and environmental agencies and Web search engines.

4. Continued the development of the capability to access Z39.50-compliant databases via the ODAS. We implemented communications between the Stanford Z39.50 client and a Wide Area Information Server (WAIS).
5. Continued development of a PC-based ODAS client using the PowerBuilder application development tool.
6. 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.
7. Demonstrated the ODAS to people from the SilverPlatter database corporation, DOE, Waste Policy Institute, and Ames Laboratory.
8. Continued to coordinate our efforts with related research efforts throughout the U.S.

Milestones and Products Projected for First Quarter, Year 4

1. Will establish a complete working ODAS at MUSC, previously the versions in Charleston have been demonstration systems only.
2. Will continue to work with MUSC's OEMO and modify the ODAS technologies to meet their needs.
3. Will begin working with Dr. Barry Weissglass (a South Carolina occupational medicine doctor) to modify the ODAS at MUSC to meet his needs.
4. Will connect to a Z39.50 database.
5. Will continue to develop EHAP's World Wide Web (WWW) home pages, integrating the latest enhancements of Hyper Text Mark-Up Language (HTML).
6. Will support the Crossroads Database with new enhancements including report generation.
7. Will demonstrate Information Systems (ODAS, WWW, and Crossroads database) to other corporations developing similar systems. Will attempt to establish collaborative agreements.