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**Environmental Biosciences Program  
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**For**

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**By The**

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## 1.0 Introduction

In May 2002, the United States Department of Energy (DOE) signed Assistance Instrument Number DE-FC09-02CH11109 with the Medical University of South Carolina (MUSC) to support the Environmental Biosciences Program (EBP). This funding instrument replaces DOE Assistance Instrument Number DE-FC02-98CH10902.

EBP is an integrated, multidisciplinary scientific research program, employing a range of research initiatives to identify, study and resolve environmental health risks. These initiatives are consistent with the MUSC role as a comprehensive state-supported health sciences institution and with the nation's need for new and better approaches to the solution of a complex and expansive array of environment-related health problems.

The intrinsic capabilities of a comprehensive health sciences institution enable MUSC to be a national resource for the scientific investigation of environmental health issues. EBP's success as a nationally prominent research program is due, in part, to its ability to task-organize scientific expertise from multiple disciplines in addressing these complex problems

Current research projects have focused EBP talent and resources on providing the scientific basis for risk-based standards, risk-based decision making and the accelerated clean-up of widespread environmental hazards. These hazards include trichloroethylene, low-dose ionizing radiation (gamma and neutron) and alpha radiation from plutonium.

Trichloroethylene research has been conducted as a joint collaborative effort with the University of Georgia.

Work on the trichloroethylene research projects has been slowed as a result of funding uncertainties. The impact of these funding uncertainties has been discussed with the DOE. Laboratory work has been completed on several trichloroethylene risk assessment projects, and these projects have been brought to a close. Plans for restructuring the performance schedule of the remaining trichloroethylene projects have been submitted to the department. A comprehensive manuscript on the scientific basis of trichloroethylene risk assessment is in preparation.

Work on the low-dose radiation risk assessment projects is also progressing at a slowed rate as a result of funding uncertainties. It has been necessary to restructure the proponency and performance schedule of these projects, with the project on Low-Dose Radiation: Epidemiology Risk Models transferred to DOE Office of Science proponency under a separate funding instrument. Research on this project will continue under the provisions of the DOE Office of Science funding instrument, with progress reported in accordance with the requirements of that funding instrument. Progress on that project will no longer be reported in quarterly reports for DE-FC09-02CH11109.

Following a meeting at the Savannah River Site on May 8, 2008, a plan was submitted for development of an epidemiological cohort study and prospective medical surveillance system for the assessment of disease rates among workers at the Savannah River Site (SRS). This project will be incorporated into the ongoing project on Population Health Risks in the Vicinity of the Savannah River Site. During a meeting at the SRS on October 21, 2008, a presentation was made on EBP participation in the development and operation of an Epidemiology Consortium at the SRS. A follow-up meeting with SRS officials is planned for 29 and 30 January 2009 at MUSC.

An epidemiology project on population health risk assessment is being conducted to assess health risks among populations in the vicinity of the SRS. This project is using the capabilities of the EBP GIS for the geographical assessment of cancer and non-cancer disease rates, as well as the potential association of population health risks with environmental exposures. Although funding uncertainties have slowed progress on some aspects of this project, it has not been necessary to restructure the performance schedule to date.

Questions, comments or requests for further information concerning the activities under this cooperative agreement can be forwarded to Dr. Lawrence C. Mohr in the EBP office of the Medical University of South Carolina at (843) 792-1532.

## **1.1 Summary and Significance of Research Projects**

### **Toxicology**

- Trichloroethylene (TCE) is the most prevalent and widespread chemical contaminant at DOE sites. TCE is regulated as a human carcinogen based upon its hepatocarcinogenicity in a crude mouse model. Very little is known about the molecular mechanisms of carcinogenesis and the human health effects of TCE. MUSC has developed a comprehensive research program on the molecular mechanisms of disease pathogenesis and the human health effects of TCE to better understand the risks to workers at DOE sites. Through this research program, MUSC has helped to ensure that TCE risk assessment and TCE remediation activities are based upon sound science. However, as a result of funding uncertainties, research on TCE risk assessment has been significantly slowed and several projects have been brought to completion. Both the Medical University of South Carolina and the University of Georgia have provided institutional support for EBP investigators to publish the results of TCE risk assessment research performed through this cooperative agreement.

### **Radiation Risk Assessment**

- The adverse health effects of both ionizing and non-ionizing radiation are of concern to DOE and the public. Many important questions about the adverse human health effects of low-dose and low-dose rate radiation exposures remain unanswered – especially with respect to cancer risks. MUSC has developed a comprehensive research program for the study of the effects of low-dose and low-dose rate radiation exposures on human health. Radiation risk assessment projects have included the development of biologically-based models of cancer risk and epidemiological models of health risks following low-dose radiation exposures. The project on epidemiological risk models will be conducted through a separate DOE Office of Science funding instrument in the future. A project is also being conducted on the assessment of both cancer and pulmonary fibrosis health risks following plutonium exposure.

### **Population Risk Assessment**

- Population risk studies in areas surrounding DOE sites are of utmost importance to the department and to the citizens who live in these areas. The Savannah River Region Health Information System is a very important national, regional, and DOE resource for the study of population health effects in the area surrounding the Savannah River Site (SRS). In conjunction with the Savannah River Region Health Information System, MUSC has developed an extremely powerful Geographical Information System in which databases containing health, environmental, demographic and socioeconomic data can be integrated and analyzed for specific population health risks. These capabilities are being used for the epidemiological assessment of both cancer and non-cancer health risks

among populations in the vicinity of the Savannah River Site. A plan has been submitted to SRS for development on an epidemiological cohort study and prospective medical surveillance system for the assessment of disease rates among SRS workers. In addition, planning has begun for EBP participation in the development and operation of an Epidemiology Consortium at the SRS.

## 1.2 Program Expenditures

### EBP Expenditure Summary

The table below reflects **expenditures** by budgeted category recorded for the period October 2008 through December 2008 and includes the total life-to-date for Cooperative Agreement CH11109.

<u>Budget Category</u>	<u>Current Period</u>	<u>LTD</u>
Personnel	\$ 77,000	
Supplies	269	---
Travel	---	---
Other	---	---
Subcontract	---	---
Equipment	---	---
Total Direct Costs	\$ 77,269	\$153
F & A	<u>61,000</u>	<u>\$ 71</u>
Total	\$138	\$224



## **2.0 Program Management and Development Office**

The mission of the Program Management Office is to ensure that all projects of the cooperative agreement achieve their stated goals and objectives and are carried out in an efficient and cost-effective manner. The executive leadership of the program has adopted a strategy-focused management approach that carefully aligns the resources and core competencies of the program with research priorities developed in coordination with DOE. Specific Program Management responsibilities include workplan development, budget formulation, task organization of multidisciplinary research teams, financial management, progress reporting and program review.

The Program Office reports to the Office of the Vice President for Academic Affairs and Provost. Key faculty and staff members involved in Program Management are as follows:

Principal Investigator and Director:	Lawrence C. Mohr, Jr., M.D.
Co-Principal Investigator, Environmental Toxicology:	David Jollow, Ph.D.
Co-Principal Investigator, Radiation Risk Assessment:	David G. Hoel, Ph.D.
Co-Principal Investigator, Population Health Risk Assessment:	Daniel T. Lackland, Dr.P.H.
Associate Director for Administration and Finance:	Anita G. Jefferson, B.S.
Administrative Coordinator:	Jill Canaday

### 3.0 Scientific Research

#### 3.1 Environmental Toxicology Research Projects

##### **3.1.1 Presystemic Elimination of Trichloroethylene and its Interactions with Alcohol: How Important are They at Environmental Exposure Levels?**

**Project Director:**

James V. Bruckner, Ph.D.

#### **Executive Summary**

Although extremely high doses of trichloroethylene (TCE) are required to produce tumors in mice and rats, there is concern on the part of the EPA and others that even trace (i.e., environmental) levels may present a cancer risk to humans. The human body has a number of processes to protect against such low level toxic insults, including first-pass, or presystemic elimination. Volatile organic chemicals (VOCs) such as TCE that are absorbed from the gut are subject to metabolism by the liver and exhalation by the lungs, before they reach the arterial circulation and are distributed systemically. It has been theorized, but not demonstrated experimentally, that all of low oral doses of VOCs are removed by presystemic elimination. It will be necessary to develop very sensitive analytical techniques in order to conduct experiments with environmentally-relevant levels of TCE. Demonstration [experimentally and by physiologically-based pharmacokinetic (PBPK) modeling], that all of low oral doses of TCE are eliminated, would have a profound effect on extrahepatic cancer and non-cancer risk assessments of TCE.

Alcohol (i.e., ethanol) and a number of other compounds are known to stimulate formation of increased amounts of cytochrome P450 2E1 (CYP2E1) in the liver. CYP2E1 is the key enzyme that initiates the oxidation of low doses of TCE to potentially mutagenic metabolites. Thus it is reasoned that drinkers metabolically activate a greater percentage of their systemically-absorbed dose of TCE to carcinogenic metabolites. Similarly, populations with genetically-determined elevations of CYP2E1 might also be anticipated to be at increased risk. The EPA uses this reasoning in their most recent health risk assessment of TCE, to support their choice of the most conservative (i.e., linear, no-threshold) mathematical model to predict cancer risks. Preliminary PBPK modeling efforts suggest that elevated CYP2E1 activity will not result increased metabolism of low, environmentally-relevant doses of TCE. Every human has CYP2E1 activity far in excess of that necessary to metabolize all of low doses. Since all of trace amounts of TCE are metabolized, it is reasonable to conclude that increased metabolic capacity due to alcohol, drugs, genetics, etc. is inconsequential. Laboratory experiments and PBPK modeling will be carried out to prove this hypothesis.

#### **Relevance**

As described above, this research project is directly relevant to current and proposed EPA regulatory standards for drinking water contamination by TCE. The EPA concludes, through both its cancer and non-cancer risk assessments (EPA, 2001), that exposure to

even minute levels of TCE is associated with low-level human risks. It is concluded that certain subpopulations with genetically- or drug-induced elevations of P4502E1 (the enzyme responsible for formation of toxic metabolites of TCE) will be at significant risk. Preliminary research with other well-metabolized chemicals indicates that this is not true. The proposed research with alcohol should definitively establish this for TCE. The second low-dose phenomenon to be investigated here will be presystemic, or first-pass elimination. The liver and lungs act in concert to eliminate ingested VOCs before they reach the systemic/arterial circulation. It is postulated that virtually all of trace levels of TCE in drinking water are removed, before they reach and present a hazard to extrahepatic target organs such as the lungs and kidneys. Experiments have been designed and a PBPK model will be developed in collaboration with Dr. Fisher to characterize the capacity of this protective mechanism under different TCE exposure conditions.

### **Objectives**

1. Develop and validate assays of TCE and its major metabolites in biological samples, including blood, tissues and urine. The assays should be sufficiently sensitive to utilize in animal experiments employing very low doses of TCE.
2. Accurately determine the capacity and dose-dependency of presystemic elimination of orally-administered TCE. Characterize the influence of dose and dosage regimen on the systemic disposition/effects of TCE and related VOCs.
3. Establish the influence (or lack thereof) of ethanol on the metabolic activation of low oral doses of TCE. Determine whether the ratio of the metabolites trichloroacetic acid (potentially carcinogenic) and trichloroethanol (non-carcinogenic) is altered by ethanol.

Specific Aim 1. To determine the capacity and dose-dependency of presystemic elimination of ingested TCE and to delineate the relative contribution of the liver and lungs.

Specific Aim 2. To establish the influence (or lack thereof) of ethanol on the metabolic activation of environmentally-encountered doses of TCE.

Specific Aim 3. To determine whether the ratio of the metabolites trichloroacetic acid (TCA) (potentially carcinogenic) and trichloroethanol (TCOH) is altered by co-ingestion of ethanol.

### **Quarterly Accomplishments**

Work on this project has been delayed as a result of an interruption in funding. Significant accomplishments to date are as follows:

1. One of our two original Specific Aims was to establish the influence (or lack thereof) of ethanol on the metabolic activation of trichloroethylene (TCE), including alteration of the ratio of its metabolites trichloroacetic acid (TCA) (a mouse carcinogen) and trichloroethanol (TCOH). Experiments during the initial year of the project established that ethanol did indeed enhance the metabolism of relatively high doses of TCE to TCA and TCOH. We hypothesized that induction of the hepatic cytochrome P450 (CYP) isozyme 2E1 (i.e., CYP2E1) would enhance the metabolism of high, but not low, environmentally-encountered doses of TCE. Upon consideration of our results and experimental design, it became evident that ethanol was not only inducing CYP2E1, but altering alcohol and aldehyde dehydrogenases (ADH and ALDH), two enzymes responsible for conversion of the intermediate TCE metabolite, chloral hydrate, to TCOH and TCA. Therefore, we chose to use pyridazine (PZ) rather than ethanol for the next phase of the project. PZ is a potent CYP2E1 inducer, but has relatively modest effects on ADH and ALDH.
2. Of particular importance to TCE risk assessment are two (2) important findings (1) PZ pretreatment resulted in a dose-dependent increase in the rate of TCE elimination, a substantial decrease in blood TCA levels and a modest increase in TCOH levels in TCE-dosed rats. These alterations were pronounced in animals given 200 mg TCE/kg orally, but barely manifest at 10 mg TCE/kg, the lowest dosage administered. These results support the aforementioned hypothesis about a lack of influence of CYP2E1 induction on low TCE doses. A gas chromatography-mass spectrometry (GC-MS) method has been developed that will allow us to continue these experiments with much lower (i.e., environmentally-relevant) TCE exposures; (2) The marked reduction in blood TCA levels (noted above) in CYP2E1-induced animals implies that liver cancer risks may be lower under such conditions.
3. The primary focus of our work on this project has been on clarifying the mechanistic basis for the substantial decrease in blood TCA concentrations in PZ-induced rats. Progress on bringing this aspect of the project to completion has been delayed by funding uncertainties.
4. The results of one study indicate that PZ pretreatment of rats results in a significant increase in the rate of clearance of TCA from the bloodstream. Half-lives ( $t_{1/2}$ ) of TCA in uninduced rats given 50 mg TCA/kg iv in two experiments were found to be ~800 and 930 minutes. The  $t_{1/2}$  of TCA is much longer (3,300 minutes) when it is formed as a metabolite in TCE-dosed animals. This indicates that TCA is a rate-limited metabolite of TCE. PZ-induced rats that received 50 mg TCA/kg iv exhibited a TCA  $t_{1/2}$  of ~240 minutes (versus the 800- and 930-minute  $t_{1/2}$ s in uninduced rats). This phenomenon may have resulted from: increased metabolism of TCA to dichloroacetic acid (DCA) and/or other metabolites; induction/activation of organic anion transporters in the kidneys; and/or displacement of TCA from plasma binding sites by PZ. Equilibrium dialysis experiments have shown that PZ's ability to displace TCA from rat

plasma proteins is quite limited. The highest PZ concentrations displaced only 20% of bound TCA. This alone cannot account for the pronounced increase in TCA clearance *in vivo*. Experiments are planned to assess the influence of PZ on urinary elimination of TCA.

5. A study has also been initiated conducted to learn whether PZ pretreatment influences: metabolism of CH to TCA versus TCOH; and conversion of TCOH to TCA. In the latter case, rats were given 50 mg TCOH/kg iv, and blood TCA profiles monitored for a period of hours. TCA concentrations in blood were substantially lower over time in PZ-induced rats than in uninduced rats. This may be due to decreased metabolism of TCOH to TCA and/or increased urinary excretion of TCA. *In vitro* experiments are planned to determine whether the former occurs. Again, work on this aspect of the project has been significantly delayed because of funding uncertainties.
6. New methodology for the determination of trace levels of trichloroethylene in biological samples using headspace solid-phase microextraction gas chromatography and negative chemical ionization mass spectrometry have been developed. The efficacy of this technique has been demonstrated and research findings have been reported in the scientific literature, as previously reported.
7. The project director has contributed to the writing of a comprehensive manuscript on the scientific basis of trichloroethylene risk assessment.

### **Performance Schedule and Status of Aims**

Work on this project has been delayed because of an interruption in funding.

The performance schedule of this project has been restructured as a result of funding uncertainties. No significant changes in the specific aims of the project are anticipated. Data analysis and manuscript publication are continuing with institutional support from the Medical University of South Carolina and the University of Georgia. A comprehensive manuscript on the scientific basis of trichloroethylene risk assessment is in preparation.

### **3.1.2 PBPK Modeling of Toxic Metabolites of Trichloroethylene in Rats, Mice and Humans: Predicting the Health Risks Posed by Low Level Exposure to TCE**

**Project Director:**

Jeffery W. Fisher, Ph.D.

#### **Executive Summary**

Trichloroethylene (TCE) remains one of the most common ground water contaminants found in the US because of its disposal and use practices by the private sector, DOE and DOD. The projected costs for remediation of TCE in the federal sector is well over \$1 B. The health risks of TCE were recently reviewed by several scientists and published as a monologue in an Environmental Health Perspectives (EHP) Supplement (Vol. 108(2), 2000). Since the EHP publication on TCE, the US EPA released a draft 'regulatory risk assessment for TCE' to the authors of the EHP monologue and asked the authors to comment on their document. In July 2002 the US EPA convened a scientific review panel to review their most recent draft TCE document. Physiologically based pharmacokinetic (PBPK) models were used as an aid in dose-response assessment (risk assessment) for cancer and non-cancer toxicological endpoints. Five PBPK models were used on various human and rodents studies for cancer and non-cancer endpoints. Several data gaps were identified as the US EPA attempted to use the PBPK models of Fisher, Clewell and Barton. In some cases the PBPK models were inappropriately or insufficiently exercised. The objective of this project is to develop a single robust PBPK model for TCE for rodents and humans by incorporating new metabolic and kinetic data published since 1999, and by conducting limited critical metabolic and pharmacokinetic experiments in rodents to fill data gaps. The refined PBPK model for TCE and metabolites in laboratory animals and humans will be exercised in an appropriate manner, and the results will be used to reduce the uncertainties associated with assessing the human health risks posed by low-level environmental exposure to TCE.

Much progress has been achieved in understanding the quantitative aspects of metabolism of TCE in humans and rodents and in understanding the toxic and carcinogenic potential of the acid metabolites that are formed from metabolism of TCE. PBPK models have progressed from models that simply describing the parent chemical to PBPK models that contain sub models describing the formation and kinetics of metabolites such as trichloroacetic acid (TCA), trichloroethanol, chloral hydrate and in some cases, dichloroacetic acid. Colleagues of mine and I have developed and published most of the PBPK models for TCE and metabolites in humans and rodents with financial support from the USAF, US EPA and Strategic Environmental Research and Development Program (SERDP). The US EPA used early-unpublished versions of our most recent PBPK models for mice and humans in their current draft risk assessment document.

#### **Relevance**

The scientific issues related to determining the health risks posed by low levels of TCE in the environment are relevant to many other solvents found in water supplies. If sound

science and extrapolation methodology can be demonstrated for this chemical, then other chemicals can be evaluated in a similar manner. This could lead to a potential saving of multiple millions of dollars in unnecessary clean-up costs.

## Objectives

1. Harmonize current PBPK models used by the US EPA into one PBPK model for TCE and metabolites. Incorporate newly published and unpublished data in humans and rodents. New data sets include published and unpublished rat data on first pass metabolism of TCE from the laboratory of Dr. Jim Bruckner at the University of Georgia, published human and unpublished rat data on glutathione conjugation of TCE [(S-(1,2-Dichlorovinyl) Glutathione (DCVG)] obtained by Dr. Larry Lash at Wayne State University, and published Epidemiology studies performed in Europe, where urinary excretion of TCA was quantified.
2. Conduct laboratory studies to refine PBPK model predicted dose metrics in laboratory animal and humans that will be used in the formulation of the final product of this project, namely a TCE human health risk assessment. Determine the stoichiometric yield of DCVG for relevant doses of TCE in rats. Information on DCVG will provide data to develop the DCVG pathway in a PBPK model for TCE and to offer plausible dose-metrics that can be associated with the risk of kidney cancer in humans. Colleagues and I have time course data for DCVG in humans exposed to TCE vapors [Lash, LH, DA Putt, WT Brashear, R Abbas, J Parker and JW Fisher. 1999. Identification of S-(1,2-Dichlorovinyl) Glutathione in the Blood of Human Volunteers Exposed to Trichloroethylene. *Toxicol. Environ. Health Part A*, 56, 1-21].
3. Conduct laboratory studies to evaluate how much dichloroacetic acid (DCA) is formed metabolically from TCE. This minor metabolite remains an important risk assessment issue because of its carcinogenic potency and the requirement that the US EPA account for cumulative risks. DCA is the number one by-product from chlorination of water. Thus, to account for the health risks poised by TCE in drinking water, the health risks from exposure to DCA itself must be quantified and accounted for in the health risk assessment of TCE.
4. Perform a cancer and non-cancer risk assessment for TCE using the harmonized single PBPK model for TCE and metabolites. The risk assessment will rely on 'mode of action' hypotheses and theoretical assumptions for low dose extrapolations. Relevant human data sets will be incorporated into the analyses.

Specific Aim 1. To harmonize current PBPK models used by the US EPA into one PBPK model for TCE and metabolites by incorporating newly published and unpublished data in humans and rodents.

Specific Aim 2. To examine the metabolism of TCE in rodents with emphasis on the dose-dependence of conversion of TCE to DCVC.

Specific Aim 3. To re-examine the dose-dependence of conversion of TCE to DCA in laboratory animals.

Specific Aim 4. To perform a cancer and non-cancer risk assessment for TCE using the harmonized single PBPK model for TCE and metabolites.

### **Quarterly Accomplishments**

Work on this project has been delayed as a result of an interruption in funding. Significant accomplishments to date are as follows:

1. Human Dichloroacetic acid PBPK model: A model structure and metabolic descriptions of DCA were patterned after work in our laboratory with the development of a PBPK model for DCA in rats and mice. The Michaelis-Menten affinity constant for GSTz ( $K_m$ ) and enzyme degradation rate ( $K_{de}$ ) in the model were fixed. The initial maximum velocity of GSTz for metabolism of DCA ( $V_{maxc}$ ), the non-metabolism loss rate ( $K_{fc}$ ), inhibition rate ( $k_d$ ) and oral absorption rates were estimated through fitting DCA blood kinetic data sets from different human clinic studies.

Several published kinetic studies exist for DCA. Additionally, we are using new unpublished low dose pharmacokinetic data collected with 8 males and 8 females under an EPA grant at Battelle NW. These individuals were given a single iv dose (0.3 mg/kg) followed by a 2 mg/kg oral dose at the beginning of the study and then repeated 14 days later. The subjects drank 0.02 mg/kg DCA for 14 consecutive days between the two doses.

The human DCA kinetic model suggests the polymorphic forms of GSTz and oral absorption rates influence the kinetics of DCA. Our simulations also suggest that DCA is degraded by another unknown metabolic pathway as proposed in our DCA modeling with rats and mice.

2. Two trichloroacetic acid (TCA) modeling papers are being finalized for publication to journals. One paper describes the influence of serum protein binding on the dosimetry of TCA in liver of mice and humans. The other paper evaluates the pharmacokinetic evidence that TCA is the primary metabolite responsible for liver tumors in mice.
3. A quantitative evaluation of the kinetics of dichloroacetic acid in humans has been completed.
4. A physiologically-based pharmacokinetic model for dichloroacetic acid and its potential role in human toxicity has been completed. The results of this investigation have been published in the scientific literature, as previously reported.
5. The project director has contributed to the writing of a comprehensive manuscript on the scientific basis of trichloroethylene risk assessment.



## Performance Schedule and Status of Aims

Work on this project has been delayed because of an interruption in funding.

The performance schedule of this project has been restructured as a result of funding uncertainties. No significant changes in the specific aims of the project are anticipated. Data analysis and manuscript preparation are continuing with institutional support from the Medical University of South Carolina and the University of Georgia. A comprehensive manuscript on the scientific basis of trichloroethylene risk assessment is in preparation.

## 3.2 Radiation Risk Assessment Projects

### 3.2.1 Low Dose Radiation: Biologically-Based Models of Cancer Risk

**Project Director:**

David G. Hoel, Ph.D.

#### Executive Summary

The use of experimental animals in radiation risk estimation is especially important for those situations when human data are inadequate or unavailable. This is particularly true for neutron exposures and low-dose rate exposures to gamma and x-ray. The purpose of this project is to apply biological based models to radiation risk estimation using experimental data.

The important questions to be answered are 1) whether or not non-cancer effects such as cardiovascular disease (CVD) are effected by low doses of radiation. 2) What is the increase in risk for a equivalent dose of alpha or neutron compared to gamma or x-ray? 3) Is the risk of chronic radiation exposure the same as that of acute exposure of both high LET (alpha, neutron) and low LET (gamma, beta, x-ray) exposures. 4) Are cancer and non-cancer effects present at low doses of radiation (neutron, alpha and gamma)?

#### Relevance

By comparing the two stage clonal expansion models for cancer with the *in vivo* experimental data, the investigators will not only increase understanding of cancer development following low-dose radiation exposure, but also add biological credibility. This approach will provide a method for answering the important environmental question of whether risks are decreased with decreasing dose-rate, a key issue for chronic radiation control of workplace exposures. Further, the effects of neutron and alpha exposure at low-doses is of importance to radiation workers.

## Objectives

The objective of this project is to determine the effects of dose-rate and radiation type on the development of various cancer types following low-dose radiation exposures. Two-stage biologically based risk models will be used for analysis and compared with the results from traditional methods of analysis. Using previously validated data, assumptions made about the biological effects of ionizing radiation can be used in the two-stage model to predict dose-rate effects on the development of various cancers following low-dose exposures. Additionally non-cancer effects such as cardiovascular disease will be estimated at low doses of radiation.

Specific Aim 1. To use the large Argonne National Laboratory Janus mouse study to answer basic questions concerning dose-rate and radiation type effects on cancer. This involves over forty thousand mice exposed acutely and chronically at several doses with both gamma or neutron exposures.

Specific Aim 2. To use the data from new studies at the Bologna Institute of Oncology (Italy) on gamma exposed Spague-Dawley rats. This data will provide for the estimation of low-dose effects of gamma exposures. These studies involve both acute and chronic exposures.

Specific Aim 3. To use this data from the Harwell Laboratory (U.K.), which involves alpha and beta radiation by inhalation and injection exposures to mice. These studies provide an accurate comparison of the cancer effects of alpha exposure to that of beta.

## Quarterly Accomplishments

1. Data analysis using the two-stage clonal expansion (TSCE) model is progressing. We are applying the TSCE model to available mouse data from the Argonne National Laboratory to operate improved cancer risk estimates for gamma and neutron exposed animals. A manuscript has been completed and is undergoing revision prior to submission.
2. Analyses of lung, liver and bone cancer incidence in beagle dogs after exposure via inhalation to  $^{238}\text{PuO}_2$  and  $^{239}\text{PuO}_2$  using a multistage cancer model are completed and a draft manuscript is being edited for submission to Mathematical Biosciences.

## Performance Schedule and Status of Aims

Neither the performance schedule nor the status of aims has changed.

### **3.2.2 Health Risks of Plutonium Exposures**

**Project Director:**

David G. Hoel, Ph.D.

#### **Executive Summary**

Human data on health risks associated with internal exposure to radionuclides (by inhalation and/or ingestion) is limited. With regard to plutonium exposures, there have been two DOE worker studies and, more recently, several studies of Russian nuclear workers (Mayak). One of the DOE worker cohorts (Rocky Flats) contains data that may be very useful in understanding the carcinogenic effects of low-dose plutonium exposure. In contrast to the paucity of human data, there is a considerable amount of experimental data related to the development of cancer in rats and dogs following plutonium inhalation. A statistical model of cancer risk following low-dose plutonium exposure is becoming increasingly important with respect to planned DOE material disposition activities, both domestic and international. For example, plans to eliminate surplus U.S. plutonium during the next two decades, through the irradiation of mixed oxide fuel and the conversion of a certain portion of the material to an immobilized waste form, represent significant program initiatives. It is particularly important for potential health effects of these initiatives to be investigated and to be incorporated into evolving statistical risk models. U.S. data will be related to prior studies of the Mayak workers which have consistently shown a higher level of lung, liver and bone cancer in comparison to U.S. workers. Pulmonary fibrosis is also a risk from the inhalation of plutonium; factors related to this risk will be assessed through the analysis of available animal and human data.

#### **Relevance**

The processing and storage of plutonium requires a quantitative understanding of the health risks of plutonium, particularly in the low-dose range. Furthermore, DOE workers who may be exposed to plutonium should be monitored with a state-of-the-art medical surveillance program that includes the use of validated biomarkers.

#### **Objectives**

1. The general problem we are considering is the evaluation and protection of the health of DOE workers in their handling of plutonium at the SRS and other DOE facilities. The project will develop risk models of the cancer and non-cancer health effects of low dose plutonium exposures, to include low-dose exposures by inhalation or ingestion. These risk models will be used for the subsequent development of an appropriate medical and environmental surveillance system.
2. The first step is a quantitative evaluation of the human and animal data so that we have good productive risk models.

3. We will develop a medical and environmental surveillance system which includes the use of urine analyses for the measurement of internal plutonium levels.

Specific Aim 1. To develop human risk models for cancer and non-cancer health effects of plutonium exposure, to include low-dose exposures by inhalation or ingestion.

Specific Aim 2. To develop a medical and environmental surveillance system for DOE workers who may be exposed to plutonium, to include low dose exposures by inhalation or ingestion. This system will be based upon the risk models developed in Specific Aim 1.

### **Quarterly Accomplishments**

1. Analyses of lung fibrosis and lung cancer incidence using data on beagle dogs exposed via inhalation to  $^{238}\text{PuO}_2$  and  $^{239}\text{PuO}_2$  have been completed. A manuscript will appear in the March issue of Health Physics.
2. Analyses of lung, liver and bone cancer mortality in beagle dogs exposed to  $^{238}\text{PuO}_2$ ,  $^{239}\text{PuO}_2$ , and  $^{239}\text{Pu}(\text{NO}_3)_4$  based on models derived from data on human exposures at the Mayak Production Association have been conducted. A manuscript has been drafted and is undergoing revision.
3. A biologically-based two-stage clonal expansion model for cancer risk has been applied to the plutonium exposed beagle dog lung cancer data and a draft manuscript has been completed.

### **Performance Schedule and Status of Aims**

Neither the performance schedule nor the status of aims has changed.

### 3.3 Population Health Risk Assessment Project

#### 3.3.1 Population Health Risks in The Vicinity of the Savannah River Site

**Project Director: Daniel Lackland, Dr.P.H.**

##### **Executive Summary**

We have developed the infrastructure, resources and technical expertise necessary to conduct epidemiological assessments of population health risks using a geographical information system (GIS). Our sources include the following:

##### *Savannah River Region Health Information System (SRRHIS)*

The geographic cancer registry incorporates 25 counties around the Savannah River Site. Cancer incidence data obtained in a high quality manner is an essential component of epidemiological investigations.

A direct link to this resource has been established in which cancer cases are geographically identified and incorporated in the data analysis. SRRHIS provides the cancer-related component of the assessment system. Cancer incidence and mortality rates are analyzed with respect to various aspects of population characteristics, demographic data and environmental exposures.

##### *Geo-coding System*

The ability to ascertain and analyze health-related, environmental, and socio-economic data for small areas, such as a census block, is an essential component of epidemiological investigation. A Geographic Information System (GIS) defines geographic study areas by organizing small areas such as census blocks. The system consists of computerized databases structured to a defined geographic area combining the tools for thematic map generation, proximity analysis, buffer zone identification and map overlay comparisons.

A critical component of any GIS is the ability to “address match” other databases into the system. An efficient GIS with a high match record must incorporate a system to add new addresses and changes, which requires an elaborate system of updates. In addition to collecting new data, epidemiological investigations are greatly enhanced with the use of existing data, saving money and time. Such databases, however, must be comprehensive and include multiple health outcomes, co-morbidities, indicators of socio-economic status, environmental exposures and population demographics and characteristics.

The analytical assessment of disease patterns constitutes a critical stage in the investigation of the environmental etiology of disease. The assessment involves the use of resources such as the GIS and multiple databases. Analyses involve a complex and sophisticated quantitative methodology.

### *Existing Databases*

The Project has established access links to various health and environmental data bases including the SC Medicaid and Medicare data bases, hospital discharge and billing data, census TIGER files, as well as data and tissue specimens from cohort studies such as the Evans County Heart Study. The Project also maintains the capability to collect new data and tissue samples.

### **Objectives**

1. To develop a comprehensive population risk assessment system and associated protocols.
2. To conduct several epidemiology risk assessments of populations in the vicinity of the Savannah River Site (SRS) using the resources of the comprehensive system.
3. To establish and maintain a state-of-the-art information system that interfaces with the agencies and custodians of health, environmental, geographic demographic and economic databases in order to provide more accurate and comprehensive population risk assessment.

### **Specific Aims**

Specific Aim 1. To continue to develop and enhance the Geographic Information System as a tool for the conduct of population risk studies.

Specific Aim 2. To continue the analysis of population cancer risks in the vicinity of the Savannah River Site (SRS).

Specific Aim 3. To assess population health risks in relation to specific environmental hazards at SRS and other DOE sites.

Specific Aim 4. To assess health risks of former workers at the Savannah River Site.

### **Quarterly Accomplishments**

1. Refined and modified manuscript regarding multiple exposures from former SRS workers.
2. Developed maps of lupus in SC and maps of relevant environmental exposures. Have begun the analysis of lupus rates among populations in the vicinity of SRS.
3. Completion of an assessment of cardiovascular disease and aortic calcification for former SRS workers.

4. Planned manuscripts and abstracts include: 1] an assessment of population disease rates and the cardiovascular disease rates of former SRS workers; 2] an assessment of environmental exposures and disease rates of lupus among populations in the vicinity of SRS; 3] cardiovascular disease among retired SRS workers; 4] assessment of multiple environmental exposures among former SRS workers.

**Performance Schedule and Status of Aims**

Neither the performance schedule nor the status of aims has changed.