NIOSH GRANTS

RESEARCH and DEMONSTRATION GRANTS FISCAL YEAR 1984

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health
NIOSH
RESEARCH AND DEMONSTRATION GRANTS
FISCAL YEAR 1984

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health
Atlanta, Georgia 30333

December 1985
DISCLAIMER

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DHHS (NIOSH) Publication No. 86-108
FOREWORD

The National Institute for Occupational Safety and Health (NIOSH) plans, directs, and coordinates a national program of research, training, and related activities to prevent occupational diseases and injuries among workers in the United States. Under the provisions of the Occupational Safety and Health Act of 1970 and the Federal Mine Safety and Health Amendments Act of 1977, research investigations constitute a principal responsibility of NIOSH. In turn the support of outstanding extramural research is a major component of this research program.

Since becoming Director of NIOSH, I have placed high priority on directing the Institute’s activities toward the most significant problems in the field. To focus our intramural efforts, we developed a suggested list of the Ten Leading Work-Related Diseases and Injuries. These priorities are also reflected in our extramural research program, which is structured to make awards in each of the areas shown on page 4 of this document.

This report is published by NIOSH to provide a readily available source of information on the status and scope of the Institute’s research grants program as a means of stimulating the development of high quality proposals for research on significant occupational safety and health problems. In this we invite the interest of scientists in the biomedical sciences, engineering, and related disciplines. Descriptions of all active grants during fiscal year 1984 (October 1, 1983, to September 30, 1984) are included, along with publications resulting from the research.

J. Donald Millar, M.D., D.T.P.H. (Lond.)
Assistant Surgeon General
Director, National Institute for
Occupational Safety and Health
Centers for Disease Control
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ANNOUNCEMENT

RESEARCH AND DEMONSTRATIONS RELATING TO OCCUPATIONAL SAFETY AND HEALTH

DEPARTMENT OF HEALTH AND HUMAN SERVICES

CENTERS FOR DISEASE CONTROL

NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH

Application Receipt Dates: New applications (February 1, June 1, October 1); Exceptions: Career Development, Small Grants, and Competing renewal applications (March 1, July 1, November 1).

The Centers for Disease Control (CDC), National Institute for Occupational Safety and Health (NIOSH) announces that competitive grant applications are being accepted for research and demonstrations relating to occupational safety and health. These include innovative methods, techniques, and approaches for dealing with occupational safety and health problems in the general industry and in mining industry.

Support in the form of project grants will be awarded for annual budget periods, within a project period not to exceed five years.

I. AUTHORITY

These grants will be awarded and administered by NIOSH under the research and demonstration grant authority of Section 20(a)(1) of the Occupational Safety and Health Act of 1970 (29 U.S.C. 669(a)(1)) and Section 501(c) of the Federal Mine Safety and Health Amendments Act of 1977 (30 U.S.C. 951). Program regulations applicable to these grants are contained in Part 87 of Title 42, Code of Federal Regulations, "National Institute for Occupational Safety and Health Research and Demonstration Grants." Except as otherwise indicated, the basic grant administration policies of the Department of Health and Human Services and the Public Health Service are applicable to this program.

II. ELIGIBLE APPLICANTS

Eligible applicants include non-profit and for-profit organizations. Thus universities, colleges, research institutions and other public and private organizations including State and local governments and small, minority and/or woman-owned businesses are eligible for these research and demonstration grants. For-profit organizations will be required to submit a certification as to their status as part of their application.
III. PROGRAM REQUIREMENTS

A. Research Project Grants

A research project grant application should be intended and designed to establish, discover, develop, elucidate, or confirm information relating to occupational safety and health, including innovative methods, techniques, and approaches for dealing with occupational safety and health problems. These studies may generate information that is readily available to solve problems or contribute to a better understanding of underlying causes and mechanisms.

B. Demonstration Grants

A demonstration grant application should address, either on a pilot or full-scale basis, the technical or economic feasibility or application of: (1) a new or improved occupational safety or health procedure, method, technique, or system, or (2) an innovative method, technique, or approach for preventing occupational safety or health problems.

C. Special Emphasis Research Career Award (SERCA) Grants

The SERCA is designed to enhance the research capability of individuals in the formative stages of their careers who have demonstrated outstanding potential for contributing as independent investigators to health-related research. Candidates must have had two or more years of relevant postdoctoral experience prior to the submission date. The application must document accomplishments in this period that demonstrate research potential; it must also present a plan for additional experience in a productive scientific environment at domestic institutions that will foster development of a career of independent research in the area of occupational safety and health. The SERCA is not intended for untired investigators, or for productive, independent investigators with significant numbers of publications of high quality, or for persons of senior academic rank (above associate professor or tenured). Moreover, the award is not intended to substitute one source of salary support for another for an individual who is already conducting full-time research, nor is it intended to be a mechanism for providing institutional support. The application must demonstrate that the award will make a difference in and enhance the candidate's development as an independent investigator.

Candidates must indicate a commitment of at least 60 percent time (not necessarily 60% salary) devoted to research under the SERCA grant, although full-time is desirable. Other work in the area of occupational safety and health will enhance the candidate's qualifications but is not a substitute for this
requirement. While working closely with one or more advisers, the awardee is expected to develop capabilities in fundamental, applied, and/or clinical research in one of the areas in section IV. At the end of the award period, evidence of independent investigative capability should be present such that the individual is better able to compete in traditional NIOSH research grant activities.

The total grant award may comprise direct costs of up to $30,000 per year and up to eight percent additional indirect costs. Direct costs may include salary plus fringe benefits, technical assistance, equipment, supplies, consultant costs, domestic travel, publication, and other costs. If the awardee already holds a small grant on the same research topic, the amount of the SERCA may be reduced up to the amount of the small grant. Awards may be up to three years and will not be renewable.

D. Small Grants

A small grant application is intended to provide financial support to carry out exploratory or pilot studies, to develop or test new techniques or methods, or to analyze data previously collected. This small grant program is intended for predoctoral graduate students, post-doctoral researchers (within three years following completion of doctoral degree or completion of residency or public health training) and junior faculty members (no higher than assistant professor). If university policy requires that a more senior person be listed as principal investigator, the application should specify that the funds are for the use of a particular student or junior-level person and should include appropriate justification for this arrangement. Though biographical sketches are required only for the person actually doing the work, the application should indicate who would be supervising the research. Small grant applications should be identified as such on the application form.

The total small grant award may comprise direct costs of up to $15,000 per year and additional indirect costs, as appropriate. The grants may be awarded for up to two years and are thereafter continuance by competitive renewal as a regular research grant. Salary of the principal investigator as well as that of the junior investigator, if university policy requires a senior person to be listed as the principal investigator, will not be allowed on a small grant, though salaries can be requested for necessary support staff such as laboratory technicians, interviewers, etc.

E. Program Project Grants

NIOSH will also accept applications for program project grants, but only after discussion with the individuals listed in this announcement.
IV. PROGRAMMATIC INTEREST

Work-related concerns of programmatic interest to NIOSH are listed below, which are applicable to all of the above types of grants. The conditions or examples listed under each category are selected examples, not comprehensive definitions of the category. Investigators may also apply in other areas related to occupational safety and health. Applications responding to this announcement will be reviewed by staff for their responsiveness and relevance to occupational safety and health. Assignment to NIOSH for funding consideration will be according to established referral guidelines. Potential applicants with questions concerning the acceptability of their proposed work should contact the individuals listed in this announcement under "FOR FURTHER INFORMATION CONTACT."

1. Occupation lung disease: asbestosis, byssinosis, silicosis, coal workers' pneumoconiosis, lung cancer, occupational asthma

2. Musculoskeletal injuries: disorders of the back, trunk, upper extremity, neck, lower extremity: traumatically induced Raynaud’s phenomenon

3. Occupational cancers (other than lung): leukemia; mesothelioma; cancers of the bladder, nose and liver

4. Severe occupational traumatic injuries: amputations, fractures, eye loss, and lacerations

5. Cardiovascular diseases: hypertension, coronary artery disease, acute myocardial infarction

6. Disorders of reproduction: infertility, spontaneous abortion, teratogenesis

7. Neurotoxic disorders: peripheral neuropathy, toxic encephalitis, psychoses, extreme personality changes (exposure-related)

8. Noise-induced loss of hearing

9. Dermatologic conditions: dermatoses, burns (scalding), chemical burns, contusions (abrasions)

10. Psychologic disorders: neuroses, personality disorders, alcoholism, drug dependency

11. Control technology research: application of scientific principles to control strategies; preconstruction review; technology forcing/new source performance concepts; technology transfer; substitution; unit operations approaches
12. Respirator research: new and innovative respiratory protective devices; techniques to predict performance; effectiveness of respirator programs; physiologic and ergonomic factors; medical surveillance strategies; psychological and motivational aspects; Effectiveness of sorbents and filters, including chemical and physical properties

V. CRITERIA FOR REVIEW

Applications will be evaluated by a dual review process. The primary (peer) review is based on scientific merit and significance of the project, competence of the proposed staff in relation to the type of research involved, feasibility of the project, likelihood of its producing meaningful results, appropriateness of the proposed project period, adequacy of the applicant’s resources available for the project, and appropriateness of the budget request.

Demonstration grant applications will be reviewed additionally on the basis of the following criteria:

- Degree to which project objectives are clearly established, obtainable, and for which progress toward attainment can and will be measured.
- Availability, adequacy, and competence of personnel, facilities, and other resources needed to carry out the project.
- Degree to which the project can be expected to yield or demonstrate results that will be useful and desirable on a national or regional basis.
- Extent of cooperation expected from industry, unions, or other participants in the project, where applicable.

SERCA grant applications will be reviewed additionally on the basis of the following criteria:

- The review process will consider the applicant’s scientific achievements, evidence of demonstrated commitment to a research career in occupational safety and health, and supportive nature of the research environment (including letter(s) of reference from advisor(s) which should accompany the application).

Small grant applications will be reviewed additionally on the basis of the following criteria:

- The review process will take into consideration the fact that the applicants do not have extensive experience with the grant process.
A secondary review will also be conducted. Factors considered in the secondary review will include:

- The results of the initial review.
- The significance of the proposed study to the research programs of NIOSH.
- National needs and program balance.
- Policy and budgetary considerations.

VI. APPLICATION AND AWARD

Applications should be submitted on Form PHS-398 (revised May 1982) or PHS-5161-1 for State and local government applications. Forms should be available from the institutional business offices or from:

Office of Grants Inquiries
Division of Research Grants
National Institutes of Health
Westwood Building - Room 449
5333 Westbard Avenue
Bethesda, Maryland 20205

The original and six copies of the application must be submitted to the address below on or before the specified receipt dates in accordance with the instructions in the PHS-398 packet:

Division of Research Grants
National Institutes of Health
Westwood Building - Room 240
Bethesda, Maryland 20205

In developing the application please note that the conventional presentation for grant applications should be used and the points identified under "CRITERIA FOR REVIEW" must be fulfilled.

An applicant organization has the option of having specific salary and fringe benefit amounts for individuals omitted from the copies of the application that are made available to outside reviewing groups. If the applicants organization elects to exercise this option, use asterisks on the original and six copies of the application to indicate those individuals for whom salaries and fringe benefits are being requested; the subtotals must still be shown. In addition, submit an additional copy of page four of Form PHS-398, completed in full with the asterisks replaced by the amount of the salary and fringe benefits requested for each individual listed. This budget page will be reserved for internal PHS staff use only.

The instructions in the Form PHS-398 packet should be followed concerning deadlines for either delivering or mailing the applications. The application should be sent or delivered using the mailing label in the Form PHS-398 packet.
The proposed timetable for receiving applications and awarding grants is as follows:

**New applications:**

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<th>Secondary Review Meeting</th>
<th>Expected Start Date</th>
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<td>October 1</td>
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**Exceptions: Career Development, Small Grants, and Competing renewal applications:**

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<td>March 1</td>
<td>June</td>
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Awards will be made based on priority score ranking and emphasis area, as well as availability of funds.

**VII. COST SHARING**

Grantees will be expected to cost share a minimum of five percent.

**VIII. FOR FURTHER INFORMATION CONTACT:**

For Technical Information Contact:

Roy M. Fleming, Sc.D.
Associate Director for Grants
National Institute for Occupational Safety and Health Centers for Disease Control
1600 Clifton Road, N.E., Bldg. 1, Room 3053
Atlanta, Georgia 30333
Telephone: (404) 329-3343

For Business Information Contact:

Leo A. Sanders
Grants Management Officer
Centers for Disease Control
255 E. Paces Ferry Rd., NE, Room 321
Atlanta, Georgia 30305
Telephone: (404) 262-6575

(This program is described in the Catalog of Federal Domestic Assistance Program No. 13.262, Occupational Safety and Health Research Grants. It is not subject to Health Systems Agency nor E.O. 12372 review.)

HHS,PHS,CDC
GLOSSARY

Grant Number - The identification number assigned to a grant application

EXAMPLE: 1 R01 OH02183-01A1

   1       R01        OH   02183   -01   A1
   _       _         _     _   ___    ___
   _      _         _     _     _     _
   Signifies a first resubmission with modifications
   Year of funding
   Sequence number for NIOSH grants
   Institute with primary assignment
   Grant Activity
   Grant Type

 Typical Codes
 Grant Type
   1 - New Competing application
   2 - Competing renewal application
   5 - Noncompeting continuation application

 Grant Activity
   R01 - Research Project Grant
   K01 - Special Emphasis Research Career Award (SERCA) Grant
   R03 - Small Grant
   R13 - Conference Grant
   R18 - Demonstration Grant
   R43 - Small Business Innovation Research (SBIR) Grant

 Institute
   OH - NIOSH

 Program Areas - Research categories of particular interest to NIOSH

 Occupational Lung Diseases (Lung)
 Musculoskeletal Injuries (Muscu)
 Occupational Cancers (Cancer)
 Traumatic Injuries (Trauma)
 Cardiovascular Diseases (Cardio)
 Reproductive Disorders (Repro)
 Neurotoxic Disorders (Neuro)
 Noise-Induced Hearing Loss (Noise)
 Dermatologic Conditions (Derma)
 Psychologic Disorders (Psycho)
 Control Technology Research (Contr)
 Respirator Research (Respir)
 Other Occupational Concerns (Other)
Aerosol Deposition in the Human Respiratory System

C.P. Yu, Ph.D.
Department of Mechanical and Aerospace Engineering
State University of New York at Buffalo
Clifford C. Furnas Hall
Amherst, New York 14260

This research is directed toward developing mathematical and computational models on aerosol deposition and clearance in the human respiratory system for occupational application. The specific aims of the project include: (i) to further establish the effects of particle factors such as shape and charge on deposition, (ii) to determine the amount and site of deposition and their intersubject variabilities, (iii) to determine mucociliary transport rates along bronchial airways, and (iv) to identify airway dimensions from particle retention data. Analytical and statistical methods will be used to achieve these goals with the extensive use of experimental data. Computer programs for deposition and clearance models will be developed and applied to a variety of exposure conditions.


Yu CP: Particle charge effect on deposition of therapeutic aerosols in the human tracheobronchial tree during inspiration. Biomechanics Symposium pp 89-92, 1981

Yu CP and Diu CK: A comparative study of aerosol deposition in different lung models. Am Ind Hyg Assoc J 43, 1982


Xu GB and Yu CP: Theoretical lung deposition of hygroscopic aerosols. Aerosols-Science, Technology, and Industrial Applications of Airborne Particles pp 981-984, 1984
TITLE

Health Risks in the Vermont Granite Industry

PRINCIPAL INVESTIGATOR

William George Brown Graham, M.D.
Pulmonary Unit P345
Mary Fletcher Unit
Medical Center Hospital of Vermont
Burlington, Vermont  05401

SUMMARY

This proposal will try to settle the question of whether low level granite dust exposure in the Vermont Granite Industry leads to adverse effects on worker health, as judged by longitudinal measurement of pulmonary function, the presence of radiographic abnormalities on chest films or the prevalence of chronic respiratory symptoms. These issues are very much in doubt. Previously published work which suggested that harmful health effects may have been in error. Serial measurements of pulmonary function will be compared with previous estimates of loss. A chest x-ray survey will establish the prevalence and type of abnormalities in the work force. Using radiographs taken in surveys since 1939, we will establish the desirable interval at which survey films should be taken. As a basis for comparison, the loss of pulmonary function and prevalence of chronic respiratory symptoms will be measured in a control group of non-dust exposed Vermont workers. Spirometric measurements, radiographic interpretations and questions regarding symptoms will observe the recently recommended standards published under the auspices of the ATS/DLD. Random sampling and analysis of total and quartz dust will be carried out using size-selective personal samplers; quartz will be analyzed using the x-ray diffraction method. Two important subsidiary questions will be examined: 1) the rate of pulmonary function loss in retired workers with radiographic silicosis, and 2) the extent to which chest films become more abnormal after dust exposure stops. The ultimate purpose of the proposal is to establish whether the more stringent standards proposed in a recent criteria document for quartz dust exposure is in fact necessary to protect worker health.

PUBLICATIONS:  None to date
Dust and Silicosis in Mining and Minerals Industries

PRINCIPAL INVESTIGATOR

Robert L. Harris, Jr. Ph.D.
Occupational Health Studies Group
Department of Environmental Sciences and Engineering
School of Public Health
University of North Carolina at Chapel Hill
Rosenau Hall 201H
Chapel Hill, North Carolina 27514

SUMMARY

Current standards and Threshold Limit Values for exposures to silica dust are based to a large extent on studies in the Vermont granite industry. Since 1935 the North Carolina State Board of Health, under authority of the North Carolina Industrial Commission, has collected environmental data to describe dust exposures in the State's dusty trades and has maintained work histories and obtained annual chest X-rays for detection of silicosis among workers employed in these trades. Approximately 4,500 environmental samples have been taken to describe dust exposures in some 200 mines and minerals industry plants. More than 200,000 chest X-rays have been taken, and 759 workers have had diagnoses of silicosis; of these, some 490 were first diagnosed in the period 1950 through 1979.

Data which have been accumulated in this mines and minerals industry surveillance program have now been systematically analyzed. The State Board of Health and the Industrial Commission have cooperated with the School of Public Health, University of North Carolina, in this analysis. Environmental and work history data have been used to develop quantitative dust exposure histories for silicosis cases and for matched non-silicotic controls. Analyses to detect and describe associations between exposures to dust and occurrence of silicosis for the various mining and minerals industries and worker populations in the North Carolina program have been done. The results of this study supplement information currently available, upon which current standards are based.

PUBLICATIONS

Rice CH: Exposure reconstruction and study of silicosis in North Carolina, Doctoral Dissertation. Department of Environmental Sciences and Engineering, University of North Carolina, 1983

PROGRAM AREA: Occupational Lung Diseases
GRANT NUMBER: 5 R01 OH01151-02
AWARD PERIOD: 09/01/82 - 08/31/85
FY83 FUNDING: $ 64,355
CUM. FUNDING: $125,161

TITLE

Activity of Amosite Asbestos and Grunerite Fiber

PRINCIPAL INVESTIGATOR

George E. Harlow, Ph.D.
Department of Mineral Sciences
American Museum of Natural History
Central Park West at 79th Street
New York, New York 10024

SUMMARY

Inhalation and/or ingestion of amosite asbestos fiber in occupational settings is associated with increased neoplastic risk. Recent data suggest that indirect occupational and household exposures may also increase the risk of developing asbestos-related diseases. Amphibole minerals occur with both asbestiform and non-asbestiform habit. Amosite (asbestiform grunerite) has been mined as asbesto, and grunerite is present in a number of common rock types, which may upon pulverization release fibers into the air. While amosite is known to produce excess malignant disease, the biological potential of non-asbestiform grunerite is unknown. The aims of this research are to examine in detail specimens of this mineral, in its range of habits, from the extensive collections of the American Museum of Natural History and from other sources. A thorough understanding of this mineral group and the interrelationships with form and occurrence is desired. Specifically, the intent is (1) to determine the physical-chemical properties of both fibrous and non-fibrous grunerite, with special attention to the mechanisms responsible for the formation of fibers, (2) to formulate a hypothesis suggesting which properties impart biological activity and which amphibole habits manifest them, (3) to establish reference minerals for biological experimentation. To achieve these goals, the specimens will be studied from the macroscopic to the most minute scale using a wide range of techniques: optical microscopy of thin sections of grunerite-bearing rocks and mineral grains; X-ray diffraction of powders (using Gandolfi and Guinier cameras and powder diffractometry); chemical analysis of these materials using an electron microprobe; SEM analysis of fragments and fibers; analytical HRTEM analysis of thinned crystals and fibers. The results will be a far better understanding of grunerite in its asbestiform (amosite) and non-asbestiform varieties, necessary for modeling factors of biological activity. The highly characterized specimens will be invaluable for biological studies.

PUBLICATIONS: None to date
PROGRAM AREA: Occupational Lung Diseases
GRANT NUMBER: 5 R01 OH01412-02
AWARD PERIOD: 09/29/82 - 08/31/84
FY83 FUNDING: $20,827
CUM. FUNDING: $59,881

TITLE

Byssinosis: The Recognition of an Occupational Disease

PRINCIPAL INVESTIGATOR

Charles Levenstein, Ph.D.
Harvard School of Public Health
665 Huntington Avenue
Boston, Massachusetts 02115

SUMMARY

The aim of this study is to research and write a history of byssinosis in the United States. By examining the history of byssinosis, we hope to elucidate conditions under which an occupational disease becomes recognized. The scientific controversy over byssinosis among cotton textile workers in the United States will be examined in its historical context by studying the roles of clinicians, including pulmonary specialists and occupational physicians, pathologists, respiratory physiologists, and later, epidemiologists, textile management, and labor organizations, relevant government agencies, and programs such as workers' compensation legislation, insurance companies, professional organizations, public interest groups as well as the interface between the health delivery system and occupational health problems. Historical materials on the textile industry and scientific research will be examined relying primarily on the materials available in New England. Since byssinosis was recognized as an occupational disease in Great Britain long before the United States, historical analysis will focus on the problems of professional communication and rival approaches to the study of disease; on the interplay of economic interests and scientific research; and on political aspects of the regulatory climate affecting occupational hazard control.

PUBLICATIONS: None to date
PROGRAM AREA: Occupational Lung Diseases
GRANT NUMBER: 5 R01 OH01605-02
AWARD PERIOD: 09/30/83 - 08/31/86
FY84 FUNDING: $ 61,518
CUM. FUNDING: $121,497

TITLE
Fiber Deposition in Human Upper Airway Model

PRINCIPAL INVESTIGATOR
David L. Swift, Ph.D.
Department of Environmental Health Sciences
School of Hygiene and Public Health
Johns Hopkins University
615 North Wolfe Street
Baltimore, Maryland 21205

SUMMARY
This is a proposal to investigate the regional deposition of airborne glass fibers in a physical model of the upper human respiratory tract including the nasal passages, or passage, pharynx, larynx, and upper trachea. Deposition fraction in these airways will be measured as a function of fiber length and diameter and air flow rate and compared to theoretical deposition fractions. Fibers of relatively uniform length and diameter are to be radiolabelled in suspension, aerosolized, and quantitatively located on the model surface with scintillation detectors.

PUBLICATIONS: None to date
PROGRAM AREA: Occupational Lung Diseases
GRANT NUMBER: 1 R01 OH02023-01
AWARD PERIOD: 08/01/84 - 07/31/87
FY84 FUNDING: $127,792
CUM. FUNDING: $127,792

TITLE

Mechanism and Treatment of Phosgene Poisoning

PRINCIPAL INVESTIGATOR

Thomas P. Kennedy, M.D.
Johns Hopkins University
315 North Wolfe Street
Baltimore, Maryland 21205

SUMMARY

Acute massive toxic gas exposure continues to be a problem facing occupational medicine and critical care medicine, not only due to isolated accidents involving workers in the manufacturing and use of chlorine, phosgene, nitrogen dioxide, ammonia, and sulfur dioxide, but also from exposure of larger bystander populations resulting from accidental toxic gas release during transportation. Much research exists on chronic low level exposure to these agents, but there is little work on pathophysiology and therapy of acute lung disease and respiratory distress from toxic gas inhalation. The proposed research will use inhaled phosgene exposure of an isolated perfused rabbit lung as a laboratory model for acute toxic gas inhalation. The pathophysiology of acute phosgene lung damage will be investigated, including whether acute broncho-constriction and pulmonary hypertension are due to lung production of arachidonic acid metabolites such as thromboxane and leukotrienes, and whether oxidant lung damage from phosgene causes depletion of lung glutathione. Several pharmacologic agents (corticosteroids, nonsteroidal anti-inflammatory agents blocking cyclooxygenase and lipoxygenase pathways, protease inhibitors, beta-adrenergic agonists, and prostaglandin E1) will be studied to determine their usefulness in attenuation lung edema formation. N-acetyl cysteine, a precursor of glutathione effective in treating oxidant liver damage from toxic dose of acetaminophen, will be evaluated as therapy for phosgene poisoning by insuring a sufficient supply of lung glutathione to react with phosgene and prevent its combination with membranes and cellular enzymes. Drugs such as the food additive antioxidant butylated hydroxy anisol (BHA) which elevate lung glutathione will be studied to determine whether chemoprophylaxis of phosgene poisoning is possible. The results of this research can provide a foundation for recommending physiologically sound therapy of oxidant lung damage from acute toxic gas inhalation in man.

PUBLICATIONS: None to date
RESPIRATORY HAZARDS OF POULTRY WORKERS

Agricultural workers are a large and understudied population. Respiratory disease appears to be a major problem in agriculture; specific respiratory illnesses recognized, include silo filler's disease, farmer's lung, atypical farmer's lung, and grain handler's illness. We have described a new respiratory hazard among swine confinement workers. As a result of this work, we have become concerned about possible health hazards among workers in poultry confinement systems. Our pilot studies suggested they experience exposures and respiratory symptoms similar to swine confinement workers. A very limited amount of data by other researchers support this supposition.

We propose the first in-depth medical and environmental study to investigate possible occupational hazards of poultry workers. The proposed investigation is a three-phase four-year study. Phase I is a 12-month effort to develop an industry-wide worker exposure profile by performing a series of walkthrough evaluations of typical turkey growing, chicken growing, hatcher, egg production, and poultry processing operations. We intend to identify and quantify the subgroups of poultry workers with the greatest potential for occupational health risks for comprehensive medical and environmental studies in phase II.

In phase II (years 2 and 3) we will recruit 400 workers for medical studies, (100 workers from each of the four subgroups of poultry workers at greatest risk). Medical assessment of these subjects will include ATS questionnaire (modified for occupational history), spirometry before and after 6 hours of work, serum precipitins, and skin testing. These data will be compared to two reference populations: 1) regionally proportioned unexposed blue-collar workers and 2) a blue-collar reference population previously studied by NIOSH. Environmental assessment of the estimated 116 work-sites and 20 control work-sites will include measurements for ammonia, carbon dioxide, carbon monoxide, total and respirable dust, and endotoxin.

Phase III, data analysis, will occur during year 4 of the study. We will examine the relationships of environmental exposures to respiratory symptoms and pulmonary function. We will also examine relationships of environmental control systems and levels of environmental contaminants. We will determine what recommendations are needed if any, to improve the work environment, to protect workers from potential health hazards, and for possible future research.

PUBLICATIONS: None to date
Program Area: Occupational Lung Diseases  
Grant Number: KO1 OH00002-01  
Award Period: 09/28/84 - 08/31/87  
FY84 Funding: $32,400  
Cum. Funding: $32,400  

Title  
Lung Collagen in Silicosis: Fibrosis Mechanisms  

Principal Investigator  
Karen Mara Reiser, M.D.  
California Primate Research Center  
University of California  
Davis, California 95616  

Summary  
Previous studies of experimental pulmonary fibrosis induced in rodents by silica, bleomycin, ozone, or paraquat suggest that collagen metabolism in silicosis differs from collagen metabolism in other types of fibrosis. In this proposal, I plan to investigate new aspects of collagen metabolism in silicosis. Specifically, I propose to conduct a detailed investigation of lung collagen crosslinking, using in vivo labelling coupled with a new HPLC technique, in three groups of rats: controls, rats exposed to silica, and rats exposed to bleomycin. Parameters to be examined include type and amount of crosslink per collagen molecule, time course of crosslink formation, turnover of crosslinks, reducibility of crosslinks, and location of crosslinks. I hypothesize that specific crosslinking patterns may act as a kind of signal, determining whether the collagen is destined to become irreversibly deposited as "fibrosis collagen" or whether it is eventually destined for degradation. I further hypothesize that lung collagen crosslinking in silicotic animals will differ from that found in both normal and bleomycin-exposed rats. Finally, I will use the data base derived from these studies to guide the development of simple urine screening assays indicative of early silicotic changes.  

Publications: None to date
TITLE

Oxygen Free Radical in Pulmonary Fibrosis

PRINCIPAL INVESTIGATOR

Marie A. Shatos, Ph.D.
Department of Pathology
University of Vermont
Burlington, Vermont 05405

SUMMARY

Exposure to asbestos and silica is associated with a variety of pulmonary disorders including pulmonary interstitial fibrosis. Although asbestososis and silicosis have been recognized as occupational lung diseases for nearly a century, the mechanism(s) by which these fibrogenic minerals induce lung cell injury and fibrosis is speculative, particularly at the cellular level.

In this proposal we hypothesize that oxygen free radicals may be an important mediator of lung cell damage and/or fibrosis in vitro and in vivo after exposure to fibrogenic minerals. To test this hypothesis, we will undertake the following studies:

1. Cytotoxicity induced by exposure in vitro to various concentrations of asbestos fibers and silicon dioxide will be determined in lung fibroblasts, alveolar macrophages and epithelial cells.

2. Production of superoxide radical (O_2^-), hydrogen peroxide (H_2O_2), and the hydroxyl radical (OH^-) by these cells after exposure to minerals at various concentrations will be monitored and correlated with results of #1 above.

3. Levels of superoxide dismutase (SOD) in lung fibroblasts, alveolar macrophages and epithelial cells after exposure to minerals in vitro and in lung sections of rats after inhalation of asbestos in vivo will be measured using quantitative biochemical assays and immunocytochemical techniques.

4. We will determine whether mineral-induced injury to alveolar macrophages, fibroblasts and epithelial cells in vitro can be prevented by the addition of scavengers of O_2^- and OH^-.

These studies will be important in elucidating the importance of oxygen free radicals in mineral-induced lung cell injury, asbestosis and silicosis. In addition, they will contribute information on possible preventative and therapeutic approaches to these serious occupational diseases.

PUBLICATIONS: None to date
PROGRAM AREA: Occupational Lung Diseases
GRANT NUMBER: 1 K01 OH00018-01
AWARD PERIOD: 09/28/84 - 08/31/87
FY84 FUNDING: $ 32,400
CUM. FUNDING: $ 32,400

TITLE
Silicosis: Immunological Abnormalities

PRINCIPAL INVESTIGATOR
Kathleen Kreiss, M.D.
National Jewish Hospital and Research Center
National Asthma Center
3800 East Colfax Avenue
Denver, Colorado 80206

SUMMARY
A population-based series of silicotic subjects was identified in an epidemiology study of respiratory disease among residents of Leadville, Colorado, in 1983. Aims of the proposed study are to compare immunologic findings in silicotic subjects, identified in the epidemiologic study, with those in community controls and in nonsilicotic miners having substantial past silica exposure. Long-term objectives are to identify immunologic factors which may predispose dust-exposed individuals to silicosis and which may predispose silicotic subjects to mycobacterial infections. Further understanding of the immunology of silicosis may suggest primary and secondary prevention measures which can be confirmed in future prospective studies. Silicotics and two appropriate comparison subjects matched for age within five years will be interviewed by a local public health nurse; will receive intradermal tests for delayed hypersensitivity to PPD, tetanus toxoid, and candida antigens; and will give a blood specimen for complete blood and differential counts, immunoglobulins, complement, immune complexes, autoantibodies, and separation of mononuclear cells. Detailed immunologic studies on peripheral blood mononuclear cells include lymphocyte proliferation to three mitogens (phytohemagglutinin, concanavalin A, and pokeweed mitogen) and to three antigens (purified protein derivative, candida, and tetanus toxoid); analysis of T-cell subsets with monoclonal antibodies to helper cells, suppressor cells, and natural killer cell phenotypes; lymphokine production, assayed for interleukin-2 and interferon; and evaluation of natural killer cell activity. Preliminary data suggest that silicotic subjects, in comparison to their wives, have decreased percentages of helper T-cells and increased percentages of lymphocytes of the natural killer cell phenotype. Immunologic differences found for silicotic subjects in comparison to dust exposed and unexposed controls will be related to profusion of small and large opacites on chest radiographs and to the presence of mycobacterial infection due to M tuberculosis or atypical mycobacteria. Silicotics wishing to have bronchoalveolar lavage in an independent study will have constituents of lavage fluid compared to T-cell phenotypes in peripheral blood.

PUBLICATIONS: None to date
PROGRAM AREA: Occupational Lung Diseases
GRANT NUMBER: 1 K01 OH00019-01
AWARD PERIOD: 09/28/84 - 08/31/87
FY84 FUNDING: $ 31,936
CUM. FUNDING: $ 31,936

TITLE

Effect of Mineral Exposure on Macrophage Function

PRINCIPAL INVESTIGATOR

Robert Clark Lantz, Ph.D.
Department of Anatomy
School of Medicine
West Virginia University
Morgantown, West Virginia 26506

SUMMARY

The effects of in vitro and in vivo (inhalation) exposure to minerals found in association with coal mine dust on function of individual alveolar macrophages will be studied. Dose-response and particle size dependent studies on functional alterations will be conducted using exposure levels which are sublethal to the cells. Two separate techniques will be used to evaluate toxic effects on cells lavaged from male Long Evans hooded rats. Electrophysiological voltage clamp experiments will be used to determine the effect of exposure on plasma membrane permeability to ions and electro-optical techniques will be used to measure the effect on production of superoxide anion, an antibacterial agent produced by the cell. In order to correlate functional alteration with exposure to minerals, backscattered electron imaging and X-ray microanalysis will also be performed on individual cells to identify those cells which have phagocytized the minerals. Because functional and electron microscopic evaluation will be done on the same individual cell, correlation between mineral exposure and functional impairment should be improved. Comparison between in vitro and in vivo exposure will permit evaluation of the feasibility of using these in vitro measurements to predict in vivo effects. This interdisciplinary approach should yield important information on the cellular sites of toxicity of minerals and should provide data to aid in assessing risks following inhalation.

PUBLICATIONS: None to date
Gas and Particle Deposition in Tracheobronchial Airways

Beverly S. Cohen, Ph.D.
Institute of Environmental Medicine
New York University Medical Center
550 First Avenue
New York, New York 10016

SUMMARY

The research proposed is the first stage of a program focused on the development and critical evaluation of quantitative predictive models for gas and aerosol deposition efficiency in lung airways in humans and animals under a variety of respiratory modes and rates. The initial objective is to develop realistic physical models of the tracheobronchial airways of humans and experimental animals. The second objective is to use the models to examine the intrabronchial dose distribution of both gases and particles. Such measurements will provide basic experimental data on pollutant mass transfer. The complexity of flow profiles in both human and animal airways precludes useful predictions of mass transfer based on current fluid dynamics theory. The physical models to be made will permit examination of particle deposition in small bronchi and bronchioles for the first time. The ultimate objective is to develop predictive models for deposition using both theory and experimentally derived coefficients, including models that account for the pronounced nonuniformity of epithelial deposition on the airways.

We propose to make single path hollow airway casts of human and dog tracheobronchial airways, including a cast composed of all major branches, a cast composed of minor branches, and a cast containing approximately equal numbers of major and minor branches. Flow distributions will be measured prior to cast pruning, and each branch removed will be replaced with an equivalent flow resistor. The casts will be fabricated so as to permit repeated assembly for experimental deposition measurements.

Aerosol deposition in the small airways will be examined for the distinctly non-uniform deposition patterns that have been previously observed in the major human airways and, more recently, at alveolar duct bifurcations in rodents. The utility of the casts for quantitative detailed gas dosimetry will be demonstrated using NO₂ as a model air pollutant and triethanolamine (TEA) as an absorbing surface. Overall deposition efficiencies at each airway segment and the pattern of deposition within airways will be defined for various constant and cyclic flow rates. Comparative measurements in these realistic flow systems with the NO₂ TEA system and with nondiffusing, noninertial particles will provide basic flow profile information needed for predictive dose estimation.

PUBLICATIONS: None to date
PROGRAM AREA: Occupational Lung Diseases
GRANT NUMBER: 1 R03 OH01677-01
AWARD PERIOD: 07/01/83 - 12/31/84
FY83 FUNDING: $14,071
CUM. FUNDING: $14,071

TITLE

Byssinosis/Chronic Bronchitis in Chinese Textile Workers

PRINCIPAL INVESTIGATOR

David Christopher Christiani, M.D.
Department of Physiology, Harvard School of Public Health
665 Huntington Avenue
Boston, Massachusetts  02115

SUMMARY

The objective of this proposal is to study the respiratory effects of exposure to cotton dust in a population of cotton, textile mill workers surveyed in Shanghai. The population selected for survey processes hand picked cotton believed to contain a lower "trash" content than most grades of machine picked cotton. Since the active agent for byssinosis is thought to be contained in the "trash" component of cotton, this population should be exposed to dust which is less active in producing acute or chronic respiratory effects. The study group has been exposed to reasonably low dust levels since the introduction of dust controls approximately 20 years ago. This long history of stable exposures along with a reasonable range of exposure will permit the examination of exposure-effect relationships. These can be compared to those published in comparable study populations. (In particular, this study design is similar to Merchant's, which provides the basis for the current U.S. standard). Selected for study were two textile mill populations; one exposed to cotton dust (445 cotton mill workers), and the other unexposed (485 silk mill workers). The field survey data were collected during an exchange program between Harvard School of Public Health and Shanghai First Medical College and included demographic data, smoking history, standardized symptomatic history (MRC for chronic bronchitis and Schilling for byssinosis), and pulmonary function measurements (forced expiratory efforts on ATS approved equipment) before and after a work shift preceded by 2 days away from work. Environmental dust sampling was simultaneously conducted, using the Lumsden Vertical Elutriator, in all job groups under study (opening through spinning). Request for support is directed at the analysis of these data: 1) to examine the prevalence of byssinosis and chronic bronchitis in the cotton workers with respect to exposures and jobs controlling for confounders and examining interaction with cigarette smoking, 2) to compare the prevalence of chronic bronchitis among cotton textile workers with that for the control group of silk workers, 3) to quantify acute change in lung function and compare this to job and exposure levels controlling for likely confounders, and 4) to examine cross-sectional lung function in the cotton textile workers for relationship to job or dust exposure adjusting lung function using data from the silk textile workers. The methods of analysis will include multiple logistic and linear regression modeling.

PUBLICATIONS: None to date
PROGRAM AREA: Occupational Lung Diseases
GRANT NUMBER: 1 RO3 OH01684-01A1
AWARD PERIOD: 08/01/84 - 07/31/86
FY84 FUNDING: $19,125
CUM. FUNDING: $19,125

TITLE

Respiratory Disease in Beryllium Workers

PRINCIPAL INVESTIGATOR

David Kriebel, M.S.
Harvard School of Public Health
665 Huntington Avenue
Boston, Massachusetts 02115

SUMMARY

The proposed project will study the respiratory effects of long-term, low level exposure to beryllium (Be). Workers in two beryllium processing plants have been studied over periods of several years. In the proposed project this data will be analyzed to quantify exposure-response relationships for beryllium. Data were collected on 214 workers (at initial survey) at one plant, and 321 at the second. These workers were surveyed over periods of eight and six years, respectively. Exposure data are available on all production jobs in both plants, and when combined with occupational histories on each subject, these data will be used to estimate current and cumulative Be exposures. Effect data available on each subject include spirometry, blood gases, chest x-rays, and respiratory symptom reports. These data will be used to study exposure-response relationships for beryllium exposure and the various measures of lung function. Because data were collected before and after "clean ups" in both plants, it will be possible to: 1) study whether the disease is progressive, reversible, or stable after a drop in exposure; 2) address the regulatory question what effect does lowering current exposure by imposition of a standard have on those who already have considerable cumulative exposure? These analyses have implications for study of other occupational respiratory diseases in which many of the same hypotheses and data limitations arise.

PUBLICATIONS: None to date
Lung Proteases and Antiprotease in Coal Dust Exposure

Michael Po Chee Ip, Ph.D.
Mount Sinai School of Medicine of the
City University of New York
1 Gustave Levy Place
New York, New York 10029

SUMMARY

Human exposures to coal dust are associated with the development of Simple Coal-workers' Pneumoconiosis (CWP). Focal emphysema is a part of Simple CWP. This lesion has been ascribed to contraction of connective tissue fibers deposited in this locus with consequent enlargement of adjacent airspaces. Alternatively this lesion may result due to elastin lysis from elastolytic enzymes produced in either polymorphonuclear leukocytes and/or alveolar macrophages. The purpose of this proposal is to study the hypothesis that elastase and collagenase secreted by alveolar macrophages following in vivo exposure of laboratory animals to three major types of coal—anthracite, bituminous, and lignite—will create focal emphysema and Simple CWP. The ability of macrophages which have phagocytized coal dust to produce and secrete enzymes in concentrations which exceed the capacity of natural protease inhibitors a2 macroglobulin and alveolar alpha 1-anti-trypsin will be studied so as to evaluate the role of coal on protease-anti-protease balance.

The effect of chronic coal dust exposure on the macrophage proteases and alveolar antiproteases will be studied by monitoring the total amount of these substances after repeated exposures to coal dust. This will be done by analyzing the alveolar lavage fluid a2-macroglobulin and al-antitrypsin and bronchial protease inhibitor by specific radioimmunoassay. Alveolar macrophage and alveolar neutrophil elastase and collagenase will also be studied. Phagocytosis of coal dust will generate superoxide ions and other oxygen metabolites. These substances have been observed to inhibit al-AT, the major antiprotease in the alveolar environment. We will study the extent of superoxide and oxygen metabolites generated by alveolar macrophages which have phagocytized coal dust and observe the effects on the alveolar antiproteases. Inhibition of the alveolar antiproteases will create a greater potential activity for the macrophage and neutrophil proteases and therefore encourage the development of focal emphysema. The effects of well-recognized environmental pollutants such as nitrogen dioxide and cigarette smoke will be studied in conjunction with coal dust exposure in order to elucidate the effects on antiproteases and the balance of alveolar protease-antiprotease materials which may influence the development of focal emphysema of coal-workers' pneumoconiosis.

PUBLICATIONS: None to date
Respiratory Effects of Sulfur Dioxide in Corn Refiners

Ian Alexander Greaves, M.D.
Department of Physiology
Harvard School of Public Health
655 Huntington Avenue
Boston, Massachusetts 02115

SUMMARY

In 1976 and 1977 a total of 457 male corn refinery workers participated in a cross-sectional study to ascertain the respiratory effects of sulfur dioxide at low levels in the work environment. The concentrations of mass respirable particulates and water-soluble sulfates were shown to be very low. Health effects were assessed by a respiratory questionnaire and by lung spirometry. Preliminary analysis of the data indicated that prevalence rates for cough, phlegm, wheezing, and a history of chest illness all increased with increasing concentration of sulfur dioxide. Lung functions tests (FEV1, FVC) were analyzed by initially standardizing for age and height, and then the effects of smoking and sulfur dioxide were examined by multiple regression techniques. This analysis suggested that neither smoking nor sulfur dioxide exposure was detrimental to lung function in these workers.

The proposed study seeks funds to recode the original raw data and to perform further analyses. In particular, the relationships of symptoms to sulfur dioxide exposure will be studied using maximum likelihood estimates obtained from a logistic model. Further analysis of the lung function tests will be performed, using adjusted and unadjusted parameters, to explore the effects of smoking and sulfur dioxide exposure. In particular, more sensitive indices of airflow obstruction (MMEF, flows at 75%, 50%, and 25% of FVC) than the FEV1, will be derived from the original spirometographs and subjected to multiple regression analysis. The findings will provide important information on the effects of sulfur dioxide at steady, low concentrations and in the presence of very low levels of other air contaminants.

PUBLICATIONS: None to date
PROGRAM AREA: Occupational Lung Diseases
GRANT NUMBER: 5 R03 OH01756-02
AWARD PERIOD: 07/01/83 - 06/30/85
FY84 FUNDING: $ 7,985
CUM. FUNDING: $ 25,604

TITLE

Follow-up Study of Respiratory Disease in Firefighters

PRINCIPAL INVESTIGATOR

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SUMMARY

The objective of the proposed study is to evaluate the chronic respiratory effects of on-the-job exposure to toxic contaminants among firefighters. A follow-up study of a cohort (N=961) of Baltimore City firefighters will be conducted. Data collected 6 to 9 years ago on pulmonary function, respiratory symptoms, and smoking habits are available. All current pensioned and withdrawn firefighters who participated in the baseline study, participated in the follow up.

Each eligible man will be sent an introductory letter to explain the objectives of the study and the procedures involved. Voluntary participation will be sought. Inactive men will be contacted by telephone to determine a date and fire department location for data collection. Active men will be visited at the location of their current fire department assignment.

On the pre-scheduled date, each man will be asked to sign an informed consent statement. In addition to explaining the objectives and procedures, permission to review infirmary records will be requested. All participants will perform a pulmonary function test under the direction of a trained technician. FEV1, FVC, and MMEF will be calculated. Each man will also be asked to complete a self administered questionnaire covering medical history, work history, and sociodemographic variables. Respiratory symptoms and smoking habits will be obtained by an interviewer using the MRC questionnaire.

Medical records in the fire department infirmary will be reviewed and episodes of illness/absence during the follow-up period, will be abstracted. Complete job histories will be obtained from personnel records.

Rates of pulmonary function change, incidence and remission of respiratory symptoms, and of illness absence will be calculated. The prevalence of chronic bronchitis and of obstructive airways disease will be determined. The relationship between both baseline function and symptoms and early retirement will be examined.

Pulmonary function and respiratory symptom data on firefighters will be compared to similar data available from a Baltimore area general population.
comparison series. Univariate statistical techniques will be used to identify factors that are associated with each health outcome in firefighters. Multiple linear regression will be used to assess the importance of occupational factors.

PUBLICATIONS: None to date
PROGRAM AREA: Occupational Lung Diseases
GRANT NUMBER: 1 R03 OH01850-01
AWARD PERIOD: 07/01/83 - 03/31/85
FY83 FUNDING: $ 6,445
CUM. FUNDING: $ 6,445

TITLE

Aerodynamic Behavior of Platelet Aerosols

PRINCIPAL INVESTIGATOR

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SUMMARY

Deposition of particulate aerosol material in the lung has long been recognized as a source of disease and disability. Much is known of the aerodynamic behavior of spherical or nearly spherical particles under the viscous flow conditions often termed "Stokes Settling". In recent years theoretical treatments for rod-shaped particles have been refined and experimental verification obtained. Lung deposition models have been developed which utilize this information to predict aerosol deposition patterns in the human respiratory tract. Unfortunately, little is known experimentally, and practically nothing is available theoretically on the behavior of platelet or flake aerosols under the viscous flow conditions found in the small airways of the lung.

The proposed research is designed to evaluate the behavior of platelet particles in viscous flow through fluid dynamic modeling, computer simulation, and through actual settling of a micron size orthotropic aerosol.

This study represents a comprehensive approach to elucidating the aerodynamic characteristics of a class of particle shapes about which little is known. The results of this research will then be suitable for incorporation in new or existing aerosol lung deposition models.

PUBLICATIONS: None to date
TITLE

Lung Parenchymal Injury Induced by Environmental Agents

PRINCIPAL INVESTIGATOR

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SUMMARY

Paraquat, silica, and asbestos are important causes of environmental lung disease because of their widespread use and because of the large numbers of people exposed. All three agents are capable of directly injuring lung parenchyma, but they also have been shown to induce a neutrophil alveolitis in the early stage of low dose, chronic exposure. This neutrophil alveolitis precedes the classic findings of interstitial fibrosis seen after long term exposure to silica and asbestos or after acute ingestion, inhalation, or dermal exposure to paraquat.

We propose to study the mechanisms of lung injury by these agents with special emphasis towards their roles in the recruitment and activation of inflammatory cells to damage lung parenchymal even at extremely low doses. The research model will be the rat lung explant system. This model allows separation of lung tissue from host inflammatory cells while retaining the basic architectural unit of the lung, the alveolus. It has been used extensively in evaluation of high dose, acute paraquat exposure which will provide background for our studies. In our laboratory, we have used the rat lung explant system to study bleomycin, a chemotherapeutic agent with a similar mechanism of direct injury as paraquat. We have found that even low dose exposure to bleomycin results in the release of factors chemotactic for neutrophils, and that neutrophils greatly enhance lung tissue injury even at very low doses of bleomycin.

In view of the results from the bleomycin studies, the proposed studies with paraquat are important first to establish a dose response relationship of paraquat induced lung injury since inflammatory cell recruitment may cause injury at previously acceptable exposure levels. Second, the comparison of paraquat, silica and asbestos initiated, inflammatory cell mediated lung injury may reveal a common mechanism of injury by these agents at low dose, chronic exposure.

PUBLICATIONS


PROGRAM AREA: Occupational Lung Diseases
GRANT NUMBER: 5 R03 OH01865-02
AWARD PERIOD: 09/01/83 - 08/31/85
FY84 FUNDING: $ 22,966
CUM. FUNDING: $ 45,766

TITLE

Respiratory Abnormalities of Hardrock Miners

PRINCIPAL INVESTIGATOR

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SUMMARY

We propose a population-based study of a random sample of male residents of Leadville, Colorado, approximately half of whom are hardrock miners. Our aims are to compare miners and nonminers for prevalence of chronic bronchitis and other respiratory symptoms, measurements of subclinical small airways abnormalities, and measurements of obstructive and restrictive lung disease, controlling for smoking status. Any health abnormalities found for miners will be related to indices of dust exposure. Subjects will be invited to participate, on the basis of randomly-chosen block of residence, by a local outreach worker who will conduct a census of eligible persons, aged 25 through 64 years. An interviewer will record respiratory, smoking and occupational histories with a questionnaire. Physiologic evaluation will include single breath nitrogen test (closing capacity, closing volume, and slope of the alveolar plateau), diffusing capacity of the lung, and plethysmographic measurements (total gas volume, airways resistance, total lung capacity, including forced expiratory volume at 1 second, peak expiratory flow rate, flow rates at 25, 50 and 75% of the vital capacity, and maximal mid-expiratory flow rate). Quality assurance for questionnaire and physiological data will be based on retesting a 10% random sample. Work histories from miner subjects will be spot-checked against Climax Molybdenum Company personnel records and used to calculate an index of occupational dust exposure from industrial hygiene measurements for job classifications and work locations. Data analysis will be based, in part, on prediction equations for normal values of pulmonary function tests at 3100 meters, developed from data for asymptomatic nonsmokers. Our long term objectives are: 1) to clarify the physiology and health implications of industrial bronchitis for hardrock miners with silica exposure, 2) to assess whether symptom prevalence and pulmonary function abnormalities seem out of proportion for a miner group at high altitude where minute ventilation is increased, and 3) to evaluate the field use of sophisticated pulmonary physiology evaluation, such as plethysmography and single breath nitrogen tests, for occupational epidemiology.

PUBLICATIONS: None to date
TITLE

Interaction of Quartz with Biological Membranes

PRINCIPAL INVESTIGATOR

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SUMMARY

The understanding of the molecular mechanism by which quartz exerts its fibrogenic activity is the goal of this project. Quartz fibrogenesis is a two stage mechanism mediated by the alveolar macrophage. Factor(s) released by macrophages after phagocytosis of quartz causes fibroblasts to increase collagen synthesis. The ability of the quartz surface to alter the permeability of the phago-lysosomal membrane is thought to lead to the release of the collagen stimulating factor(s).

The focus of this project is on the interaction of the quartz surface with cell membranes. Specifically: (1) The importance of surface charge and hydrogen bonding ability of the quartz surface in membrane interaction, (2) Identification of compounds which inhibit this interaction, (3) Identification of quartz and membrane receptors by use of inhibitors, (4) Extension of these studies to the silica polymorphs—tridymite and cristobalite.

The pneumoconiosis and mineral-related malignancies (e.g. with asbestos) rank as one of the most important factors in occupational lung diseases. Quartz hemolysis and macrophage cytotoxicity will be used as a bioassay. Various quartz samples from different geological locations (which have been characterized for surface charge, hydrogen bonding ability, size distribution, etc.) will be used to challenge erythrocytes and macrophages. The importance of these variables in hemolysis and cytotoxicity will be determined. Inhibitors will be used to further characterize possible receptors.

This study would enable a molecular understanding of the critical step in which quartz initiates the fibrogenic sequence.

PUBLICATIONS: None to date
Etiological Factors in Industrial Low Back Injury

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Low back injury is a common condition in industry that results in considerable time loss disability with an enormous socioeconomic impact. Previous investigations into this problem have been largely retrospective and have focused on isolated parameters. The objective of the proposed investigation is to identify factors associated with time loss disability from low back injury in workers employed by a large aircraft company using a multifaceted approach. Jobs, worker, and work environment factors as well as clinical findings will be used in a prospective study of new employees. Jobs will be analyzed using a validated biomechanical model to determine if a specific task results in a load level on the lumbar spine which increases the likelihood of a low back injury. The data generated from the study will be useful to management in better aligning the task and the worker. Such modifications will improve job satisfaction for workers and subsequently diminish the impact of time loss disability from low back injury.


TITLE

Acceptable Weight of Lift for Extended Work Shifts

PRINCIPAL INVESTIGATOR

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SUMMARY

The major objective of this work is to determine the maximum weight of lift, acceptable to male and female industrial workers, for extended work shifts (twelve hours per day). The effect of box size, frequency of lift, and height of lift on this maximum weight of lift will be studied.

The psychophysical approach will be used. Thirty-seven male and 37 female subjects will be allowed to determine (subjective estimate) the amount of weight they are willing to lift for a given combination of task variables. Predictive models will be developed based on operator variables (sex, age, strength, and anthropometric variables), task variables (box size, frequency, height of lift), and shift duration (8-hours/day, 10-hours/day, or 12-hours/day).

The data generated will be integrated with some specific past studies to develop a comprehensive "maximum acceptable weight of lift" data base. The metabolic energy expenditure rate of the subjects, at the maximum acceptable weight of lift, will be measured to determine metabolic overloading in case of extended work shifts. The psychophysical approach will be validated by actually having the subjects lift weights, for some randomly selected combinations, for 8-hours and subsequently for 12 hours.

Statistical techniques and a heuristic technique (CMDH) will be used to analyze the data. It is hoped that this research will provide a basis for job/workplace design and/or proper operator-task match for extended work shifts and thus contribute in restricting overexertion injuries resulting from manual materials handling activities.

PUBLICATIONS


Mital A and Shell RL: Determination of rest allowances for repetitive physical activities that continue for extended hours. Proceeding of the 1984 Annual International Conference of the Institute of Industrial Engineers, Norcross, Georgia, 637-645, 1984


Mital A and Shell RL: Development of design data base for manual lifting activities for extended work-shifts. Proceedings of the Fall Conference of the Institute of Industrial Engineers (to appear), Atlanta, Georgia, October 1984


Mital A: Maximum weights of lift acceptable to male and female industrial workers for extended workshifts. Ergonomics 27 (8), 1984 (in press)

Mital A: Comprehensive maximum acceptable weight of lift database for regular 8-hour work shifts. Ergonomics 27 (8), 1984 (in press)

Lifting Capacity of Industrial and Student Populations

PRINCIPAL INVESTITGATOR

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SUMMARY

The major objectives of this work are: (i) to determine the difference between lifting capabilities (maximum acceptable weight of lift) of industrial and student populations, by collecting experimental data under identical conditions and (ii) to quantify patterns of these differences.

Using the psychophysical approach, 37 male and 37 female students determine (subjectively) the maximum amount of weight they are willing to lift for a given combination of task variables. Three task variables will be studied: box size, frequency of lift, and height of lift. Their levels will be identical to those used for industrial subjects. The maximum acceptable weight of lift data, generated on the student population, will be compared with similar data already collected on industrial subjects (NIOSH Grant No. 1-R01-OH01429-01), to quantify the differences.

Statistical techniques will be used to analyze differences between student and industrial workers. The pattern(s) of these differences will be used to modify results of some specific studies, conducted on students, dealing with asymmetrical loading, for the industrial workforce.

It is hoped that difference pattern(s) identified in this research will also provide a logical basis for extending the results of many other past (or future) studies, which have been (or will be) conducted on students, to the industrial population.

PUBLICATIONS: None to date
PROGRAM AREA: Musculoskeletal Injuries
GRANT NUMBER: 5R01 OH01962-02 *
AWARD PERIOD: 09/01/83 - 08/31/86
FY84 FUNDING: $129,374
CUM. FUNDING: $893,724 *

TITLE

Back Injuries: Mechanical Stresses in the Human Spine

PRINCIPAL INVESTIGATOR

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SUMMARY

A large proportion of industrial injuries result from manual materials handling and lifting tasks. Back injuries occur with great frequency, often cause acute suffering and serious disability in the workers involved, and are extremely costly to the industrial economy.

The objectives of this research are: (1) to analyze the three dimensional force systems that act on the human spine during industrial handling and lifting tasks, (2) to analyze the mechanical stresses imposed on the structures of the trunk by those force systems, and (3) to apply this information to reduce industrial injuries. Basic features of the program are: (1) the use of computer-generated analogs of the entire thoracolumbar spine and of single substructures of the trunk to make the three dimensional force analyses, and (2) the conduct of experiments to provide input data for the models, to determine when the models are valid, and to confirm predictions made from model-obtained results.

The results of these biomechanical studies should lead to significant improvements in the ability to reduce the incidence and severity of industrial back injuries.

* Previous support under Grant Number R01 OH00514.

PUBLICATIONS


Lantz SA: The mechanical effectiveness of lumbar spine orthoses. University of Illinois at Chicago, 1984 (thesis)


Spencer DL, Miller JAA, and Bertolini JE: The effect of intervertebral disc space narrowing on the contact force between the nerve root and a simulated disc protrusion. Spine 9:422-426, 1984
TITLE

Impact of Automation on Industrial Inspector Stress

PRINCIPAL INVESTIGATOR

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SUMMARY

The objective of this research is to determine how both human stress and human performance vary with the level of automation in an industrial inspection job. Industry is demanding higher quality of its workers and of its inspectors who are charged with maintaining and monitoring that quality. At the same time, sophisticated automation is becoming available to extend the human inspector's capabilities on some tasks within the inspection job. Inspection is known to be a stressful job, and with these two trends, a job which is likely to increase in stressfulness.

A machine, called a Color Video Comparator or CVC will be used to obtain six levels of inspection automation from unaided human inspection through automated display, sequencing and pacing to a pattern-recognition algorithm. Performance and task stress will be measured in a laboratory task of inspecting printed circuit boards for eight subjects at each level of automation. The procedure follows one already performed successfully at one level for the Western Electric Company. This company will supply the CVC and the circuit boards used in the study. Parts of the laboratory study will be replicated using inspectors at two Western Electric plants so that differences between task stress and job stress can be measured. The results of the project will be of value to designers of automated and semi-automated systems as they will help to specify the level of automation which gives the best balance between system performance and operator stress.

PUBLICATIONS: None to date
TITLE

Isometric vs. Isokinetic Back Lifting Performance

PRINCIPAL INVESTIGATOR

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SUMMARY

Existing knowledge of the biomechanical capabilities of the back during lifting activities is limited to static evaluation of exertions. This has resulted in ergonomic recommendations, models, and evaluative procedures which have produced little impact in the control of the low back pain (LBP) problem. The problem arose from the fact that manual material handling tasks usually require dynamic action of the biomechanical system. The objective of this research is to investigate biomechanical capability of the back in a quasi-dynamic testing procedure. An isokinetic dynamometer will be used to control the velocity of back-lifting motion about the lumbro-sacral junction. The subsequent torque production and electromyographic activity of the back musculature will be monitored. The exertions will also be considered as a function of subject age. These results will compliment existing static exertion data and facilitate the biomechanical knowledge of true dynamic lifting tasks.

PUBLICATIONS: None to date
Vibration of the Intervertebral Motion Segment

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The aim of this work is to assess the effect of loads statically or cyclically applied to the intact lumbar intervertebral motion segment in the mid-sagittal plane in vitro. The changes in the mechanical characteristics of the vertebral body-disc-vertebral body preparation will be measured. A combination of compression and flexion loads will be imparted to the preparations at a frequency of 9.5 cycles/sec. Changes in mechanical characteristics will be assessed before and after the cyclic or static load exposures via static load-deflection tests to assess three-dimensional vertebral body motion. The mechanical effect of a single overload event following the static or cyclic loading will be evaluated in a similar manner. Forty human cadaveric spine segments will be thus evaluated in a temperature and humidity controlled environment.

The long term objective of this study is to correlate the mechanical changes due to a cyclic loading of the intervertebral motion segment to epidemiologic data showing an increased incidence of herniated nucleus pulposus in seated operators in vibration environments (i.e. long haul truck drivers).

Mechanical engineering techniques will be used to evaluate the preparations as if they were materials in a mechanical fatigue environment. The results of this study may help elucidate the mechanical factors involved in the production of low back pain in a vibration environment.

PUBLICATIONS: None to date
Carpal Tunnel Syndrome - Intrinsic Risk Factors

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SUMMARY

The incidence of carpal tunnel syndrome (CTS) is increasing within the industrial setting and is one of the most disabling and costly medical problems for companies, unions, and/or employees. Attempts to minimize CTS in the workplace have included modifications in the working environment, redesigning of hand tools, and alterations in work schedules. In addition to understanding these extrinsic risk factors, the intrinsic factors in the development of CTS such as diabetes mellitus, arthritis, wrist trauma, hormonal status, and hypothyroidism have been explored in groups of patients with CTS. Our preliminary work demonstrates an additional intrinsic risk factor, namely the association between carpal canal size and CTS. Other critical measurements, such as the depth, width, and shape of the canal may also be related to the development of CTS. The carpal canal area will be studied in a detailed cross-sectional approach in order to develop an understanding of which factors affect the compression of the median nerve.

In this study, we intend to evaluate an entire group of workers who have been performing identical tasks within the same job setting. In this way we can control for work requiring hand/wrist movements. These workers will be given a battery of tests by a neurologist, including uniform clinical history, standardized physical examination, and electrodagnostic studies. Following the administration of these tests, workers will be categorized as those with and without CTS, and computerized tomography will be utilized to evaluate the size and shape of the carpal canal. It is hypothesized that these intrinsic risk factors associated with carpal canal size may play a role in the development of CTS in workers. In addition, the prevalence rate for CTS in this population of workers will be determined.

PUBLICATIONS: None to date
Quantification of Dynamic Muscle Strength

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Manual materials handling activities can cause high stresses on the musculoskeletal system. The dynamic nature of these tasks, such as lifting, preclude the use of the traditional concepts of human strength: isometric and isotonic contraction. Instead, the novel development of isokinetic muscle contraction has expanded the study of dynamic muscle strength. Isokinetic contractions occur against a leg/arm which controls the velocity of movement and offers resistance proportional to the muscle dynamic tension developing capacity at every point in the range of motion. Thus the maximum demand can be placed on the muscle at any time; by selecting appropriate velocities, muscle power can be maximized.

The proposal is to quantify the dynamic strength of those muscle groups that relate to manual materials handling activities in a four-phase research plan: (1) Investigate in detail the dynamic properties of muscle strength for those muscle groups used most often in manual materials handling activities, (2) Compare the measurement of these properties on the stationary Cybex isokinetic dynamometer with those measured on the portable Mini-Gym isokinetic dynamometer through correlation analysis, (3) Devise dynamic strength tests that would be representative of the actions and muscle groups for manual materials handling activities and that could be easily implemented for pre-employment strength testing, and (4) Compare the dynamic strength tests with existing static and psychophysical tests and with predictions from dynamic models.

None to date
TITLE

Reflexive and Tactile Effects of Hand Tools

PRINCIPAL INVESTIGATOR

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SUMMARY

Cumulative trauma disorders are a major health problem among workers in some manual industries. The purpose of this work is to investigate how handle design affects stresses in the worker's hand. It is hypothesized that handle vibration, posture, temperature, and hardness affect the onset of temporary numbness and the tonic vibration reflex for inexperienced operators. This results in the application of excessive hand grip force which contributes to the incidence of cumulative trauma disorders.

Laboratory subjects will hold a handle-shaker assembly which is equipped with a dynamometer. The onset of temporary numbness will be measured using objective tactility tests, such as two point discrimination and light touch to deep pressure identification at intervals after vibration exposure. Presence of the tonic vibration reflex will be indicated by electromyographic activity correlated with the vibration stimuli.

The relationship between handle hardness, temperature, and vibration on hand grip force will be determined. A cross-sectional study of the hand grip forces exerted by workers with varying experience operating hand tools will be made and the results obtained in the laboratory will be verified in the field.

PUBLICATIONS: None to date
PROGRAM AREA: Musculoskeletal Injuries
GRANT NUMBER: 1 R03 OH01906-01
AWARD PERIOD: 09/30/83 - 03/31/85
FY83 FUNDING: $ 15,828
CUM. FUNDING: $ 15,828

TITLE
Repetitive Trauma Disorders: Occupational Risk Factors

PRINCIPAL INVESTIGATOR
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SUMMARY
Painful and disabling disorders of the hand, wrist and elbow are associated with the repetitive or sustained exertions and movements of many work activities. These disorders include carpal tunnel syndrome, tenosynovitis, and epicondylitis.

The specific occupational causes for these disorders have been intensively studied. However, there have been few satisfactory investigations which permit reliable estimates of the incidence and prevalence of these problems in the workplace. Similarly, there have been few systematic evaluations of specific job-related risk factors.

The United Auto Workers proposes to: (1) conduct a survey of the prevalence of hand, wrist, and elbow disorders in a manufacturing environment, and (2) estimate the relative risk of different jobs, which will be ergonomically evaluated, for selected disorders.

We propose to use a succinct, briefly administered questionnaire, and limited physical examination to determine the prevalence of selected hand, wrist and elbow problems among workers in an assembly plant. Comparisons of prevalence among workers in different departments and major job assignments will be made.

A group of cases will be selected and matched with controls having no upper extremity complaints. Recent jobs performed by these workers will be observed, analyzed and categorized (in a blind fashion) according to the characteristics believed related to cumulative trauma disorders. This ergonomic evaluation will consist of a simplified and streamlined procedure derived from the more elaborate biomechanical evaluations that have already been developed by other researchers. Relative risks for these job characteristics will be calculated. Thus the second component of this research will consist of carrying out a new ergonomic job evaluation procedure, and assessing the association between that evaluation and the repetitive trauma disorders identified using a new survey instrument.

PUBLICATIONS: None to date
TITLE

Ergonomics Seminars in Material Handling

PRINCIPAL INVESTIGATOR

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SUMMARY

REASON FOR WORK:

Overexertion injuries resulting from manual handling constitute about 25% of all compensable accidents, cost about $1 billion annually, and show an increasing trend. With worker selection and training obviously ineffective, the only basic and therefore effective solution is to design the work system to suit the physical and behavioral characteristics of workers. Thus, ergonomics must be applied systematically in the design of work, (i.e. process, task, equipment, tools, etc.).

OBJECTIVE AND METHOD:

Development of special seminars for the use of Ergonomics in Material Handling. This incorporates:

1. Material Handling: Manual
2. Seminar Agenda
3. Visual Aids
4. Active Participation
5. Three Initial Seminars

PUBLICATIONS: None to date
Aflatoxin Exposures of Agricultural Workers II

PRINCIPAL INVESTIGATOR

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SUMMARY

Aflatoxins are produced by the ubiquitous fungi, *Aspergillus flavus*, often in significant quantities on corn, cottonseed and peanuts. In a previous NIOSH grant, Aflatoxin Exposures of Agricultural Workers, I R01 OH 00796-01, the authors demonstrated that the airborne dust generated when contaminated corn is handled also contains aflatoxins. This evidence coupled with the fact that aflatoxins are toxic, mutagenic, teratogenic, immuno-suppressive and extremely carcinogenic, suggest that airborne aflatoxins pose a serious inhalation hazard to a large number of agricultural workers. This study is designed to assess worker inhalation exposures to aflatoxins and viable fungi and to determine whether health records are accessible and sufficiently complete for a future epidemiology study in Georgia. The need for an epidemiology study is indicated by recent studies linking increased cancer rates with corn production which are unexplained by known factors.

The proposed study consists of four parts: 1) The development of an analytical method capable of analyzing aflatoxins in dust collected at the breathing zone of workers by personal sampling devices; 2) A field survey to determine aflatoxin inhalation exposures and doses in handling contaminated corn, cottonseed and peanuts; 3) The determination of the quantities and types of viable fungi, and 4) A feasibility study to establish if information is available for an epidemiology study to test the association of the estimated cumulative exposures to aflatoxins with the cancer rates of agricultural workers in Georgia.

Viable fungi will be collected simultaneously with many of the airborne dust samples. Mathematical relations will be sought between viable fungi counts, the aflatoxin content of the airborne dust and the aflatoxin content in the bulk corn. From these relationships and prior field surveys for aflatoxins by the U.S. Department of Agriculture, cumulative exposures for several groups for agricultural workers can be estimated. This data can serve as the basis for making decisions about the need for protective measures and to indicate the direction for future studies.
PUBLICATIONS


PROGRAM AREA: Occupational Cancers
GRANT NUMBER: 5 RO1 OH00914-05
AWARD PERIOD: 05/01/79 - 08/31/84
FY83 FUNDING: $ 201,787
CUM. FUNDING: $1,218,840

TITLE

Lung Cancer Screening of Workers at High Risk

PRINCIPAL INVESTIGATOR

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SUMMARY

A 5-year prospective health screening of 8000 coke-oven workers at high risk of bronchogenic carcinoma is proposed to (1) Evaluate the effectiveness for the early detection of lung cancer by estimating the sensitivity and specificity of serum carcinoembryonic antigen (CEA) and DNA content of exfoliated bronchial epithelial cells; (2) Contrast that effectiveness with that of concomitant screening using chest x-rays and exfoliative bronchial cytology; (3) Determine the histologic types of bronchogenic carcinoma found in these workers and to relate these findings to those above; and (4) Examine the relationship in the development of bronchogenic carcinoma between metaplasia, dysplasia and anaplasia in exfoliated bronchial epithelial cells and to correlate the cytomorphologic findings with the DNA content (ploidy) of the cells.

Baseline biologic screening tests will be performed and personal, smoking, occupational and medical histories will be obtained from all subjects at the implant medical facilities. Specimens and data will be sent to the City of Hope for analysis and evaluation. Then the screening will be performed semiannually in those workers specified by federal regulations; and annually in the others. The screening test battery will consist of a chest x-ray and samples of sputum and blood. Statistical specificity procedures will be used to evaluate the validity of these test; and "stepwise" discriminant analysis, to evaluate their cancer-screening capability over specific time periods.

The experience derived from this research will be used to formulate a medical surveillance, intervention and control strategy appropriate not only to coke oven workers, but also both to other occupational groups and to those in general community who are at high risk of developing lung cancer.

PUBLICATIONS


TITLE

Carcinogenic Properties of Nitrous Oxide

PRINCIPAL INVESTIGATOR

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SUMMARY

There is now strong evidence to indicate that the gaseous anesthetic, nitrous oxide, causes an increased incidence of tumors in operating room and dental personnel. This evidence is based mainly on a recent retrospective survey which showed that female dental chairside assistants working with nitrous oxide had twice the tumor incidence of similar groups not working with that anesthetic. Previous surveys supported this finding. Although nitrous oxide is the most widely used inhalational anesthetic throughout the world and has numerous other commercial uses, only two limited studies of its carcinogenic potential have so far been completed. The methods used in these negative studies, however, are generally considered too insensitive to give conclusive results. Thus, in light of the new epidemiological evidence, it seems imperative that the carcinogenic potential of nitrous oxide be studied as soon as possible in a complete bioassay. Therefore, the primary aim of this project is to perform in vivo studies to determine whether nitrous oxide is carcinogenic to experimental animals. A secondary minor aim is to use the results obtained to predict whether there are feasible methods for reducing the full histopathological examination in carcinogen bioassays. Preliminary studies will be performed to determine the maximum tolerated dose (MTD) of nitrous oxide. Groups of 150 Swiss/Webster mice will be exposed for 18 months to either the MTD of nitrous oxide or a subfraction of MTD. A similar control group will be exposed to air under the same experimental conditions. At or after this period, animals will be sacrificed and complete necropsy performed. Thirty-two tissues will be subjected to full histopathological examination. The number and types of tumors found will be documented and statistical comparisons made among groups. These investigations should determine whether nitrous oxide is carcinogenic to Swiss/Webster mice. It should then be possible to infer similar conclusions about risk to operating room personnel and to improve experimental design for future carcinogenicity studies.

PUBLICATIONS

PROGRAM AREA: Occupational Cancers
GRANT NUMBER: R01 OH01331-03
AWARD PERIOD: 08/01/82 - 07/31/85
FY84 FUNDING: $109,050
CUM. FUNDING: $321,625

TITLE
A Carcinogen/Mutagen Detector for HPLC

PRINCIPAL INVESTIGATOR
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SUMMARY
Techniques to exploit a detection principle that was used to screen carcinogens with a sensitivity and specificity of 88 percent are described which utilize the detection principle to monitor the workplace for biohazardous chemicals. The principle is based upon the electrophilic properties of mutagens, carcinogens, and teratogens that interact with the genetic-informational biomolecules DNA and RNA. The electrophilicity of the genetically damaging chemicals is measured by the rate at which these chemicals attach quasifree electrons. The unique transport and reaction properties of quasifree electrons provide a biochemical-physical basis for electronically measuring biohazardous chemicals, and methods to develop area and personnel biohazard monitors are proposed. The electronic detection methods are ideally suited for use in conjunction with high performance (pressure) liquid chromatography or HPLC, the most rapidly growing analytical technique. Combining the sensitivity and specificity of a quasifree electron detector with the flexibility and speed of HPLC would produce a powerful screening and monitoring system that would reduce our exposure to many exogenous biohazards and permit more equitable regulation of such hazards.

PUBLICATIONS

Bakale G. and Beck G: A Picosecond Conductivity Technique Applied to Study Excess Electron Reactions in Hydrocarbon Mixtures. ibid p. A5-01


PROGRAM AREA: Occupational Cancers
GRANT NUMBER: 5 R01 OH01379-02
AWARD PERIOD: 09/29/82 - 08/31/84
FY83 FUNDING: $ 9,142
CUM. FUNDING: $ 97,746

TITLE

Cohort Mortality Study of Textile Dyers, Finishers

PRINCIPAL INVESTIGATOR

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SUMMARY

The proposed research will establish a cohort of workers exposed occupationally in the past to textile dyes derived from benzidine, o-tolidine, and/or o-dianisidine, and/or to textile finishes containing formaldehyde. Prospective observation of their full mortality experience from the time of first exposure, will be conducted. Expected and observed rates of death by cause will be tabulated to ascertain if unusual mortality patterns exist. Such data will have importance in assessing the human carcinogenicity of dyes derived from the above substances and of finishes containing formaldehyde.

PUBLICATIONS: None to date
PROGRAM AREA: Occupational Cancers
GRANT NUMBER: 5 R01 OH01511-02
AWARD PERIOD: 09/30/83 - 08/31/85
FY84 FUNDING: $144,728
CUM. FUNDING: $267,067

TITLE
Risk of Pathologists Exposed to Formaldehyde

PRINCIPAL INVESTIGATOR
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SUMMARY
Recent studies by the Chemical Industry Institute of Toxicology (CIIT) suggest that exposure to formaldehyde vapor may be carcinogenic in rats. These findings have raised concern for the health of 1.75 million workers with occupational exposures to formaldehyde as well as persons with exposure from home insulation. This proposal is to examine the mortality experience of pathologists, a medical specialty group with formaldehyde exposure, using a non-concurrent prospective study design. Comparison populations include other physician specialists who have only limited exposure to formaldehyde. All causes of death listed on death certificates will be examined, and selected causes, notably cancers, will be verified.

PUBLICATIONS: None to date
TITLE

Occupational Exposure in Adult Glioma Patients

PRINCIPAL INVESTIGATOR

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SUMMARY

A large amount of suggestive evidence on the etiology of brain tumors has come from recent studies of the rubber, plastics and petrochemical industries. These studies suggest associations between chemical exposures and tumors of the glioma series. The proposed study will collect extensive occupational and residential histories for male and female glioma patients by interview and will compare the occupational distributions to matched neighborhood controls. Chemical exposures of interest will be followed up to identify possible agents. Data will also be collected on family history of brain tumors, radiation exposure, use of certain drugs, and a variety of socioeconomic control items.

The proposed study takes advantage of the availability for interview of a very large population of glioma patients at the Brain Tumor Research Center of the University of California, San Francisco. Supplementing these patients with patients at other member institutions of the Northern California Oncology Group, we propose to interview 500 glioma patients over a four-year period. The study will be carried out in collaboration with staff of the Northern California Cancer Program, parent organization of the Northern California Oncology Group, and staff of the Brain Tumor Research Center.

PUBLICATIONS: None to date
Production and Fate of Hydroxamic Acids in Hepatocytes

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The purpose of this program is to elucidate certain biochemical processes that are involved in the toxicity of aromatic amines and nitroso aromatic compounds. As a group the aromatic amines comprise some of mankind's most important industrial chemicals. Their extensive use as pesticides in modern agricultural practice continues to increase, yet a knowledge of their biological fate and effects in living organisms is very incomplete. Since many aromatic amines and related chemicals are known carcinogens, it is necessary that a detailed knowledge of the metabolism of these chemicals in higher animals be attained. This program will study the extent to which model aromatic amines are metabolized to hydroxamic acids, since hydroxamic acids are known to account for much of the toxicity of aromatic amines. The program will examine the biochemical processes that convert nitroso aromatic compounds to hydroxamic acids possessing unusual N-acyl groups. The specific biochemical pathways responsible for such hydroxamic acids arise from the interaction of a nitroso aromatic compound with a thiamine-dependent enzyme. Another facile, but non-enzymatic, reaction that causes the production of the N-formyl type hydroxamic acids is the reaction of a nitroso aromatic with glyoxylic acid. Primary hepatocyte cultures prepared from rats will be the principal system in which these studies will be conducted, although for comparative purposes primary hepatocyte cultures from syrian hamsters will also be used. The results of this program will provide valuable data to help design measures to minimize mankind's exposure to or damage from potentially genotoxic chemicals.

PUBLICATIONS: None to date
PROGRAM AREA: Occupational Cancers
GRANT NUMBER: 1 R01 OH02067-01
AWARD PERIOD: 09/28/84 - 08/31/87
FY84 FUNDING: $139,307
CUM. FUNDING: $139,307

TITLE
Occupational Cancer Surveillance: New Approaches

PRINCIPAL INVESTIGATOR
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SUMMARY
There is no occupational cancer incidence surveillance system in the United States today which provides population-based monitoring for a defined geographic area and across a wide variety of occupations. The proposed study has two long-term objectives: 1) to perform continuing surveillance for cancer hazards in the workplace in a cost-effective manner and 2) to reduce cancer morbidity and mortality among employment groups found to have increased risks associated with their work. Specific aims of the project are to develop and evaluate an occupational cancer monitoring system in terms of its ability to: 1) be cost effective, 2) provide useful data for both commonly occurring and rare cancers, 3) provide data regarding possible occupational cancer hazards of blacks and women, 4) evaluate smoking histories, and 5) implement an ongoing system. New leads regarding the occupational etiology of cancer will be produced.

The proposed system will complement the Metropolitan Detroit Cancer Surveillance System (MDCSS), which is a participant in NCI's SEER program. Occupational histories and related information will be obtained by telephone interview. A total of approximately 13,569 cases with newly diagnosed cancers of the lung and bronchus, colon and rectum, urinary bladder, and esophagus are projected to be interviewed during the course of the study. Cases selected for the study will include all newly diagnosed cases of the specified sites in the age category 40 to 84.

New leads about occupational risks associated with cancer incidence are expected from the proposed study, particularly for women and blacks. These leads will be immediately disseminated to local public health officials, NIOSH, and appropriate groups of workers and industries. Analytic investigation suggested by study results will follow immediately as well. Thus, the proposed system will provide both descriptive data and immediate translation into occupational health interventions and analytic studies as warranted. Finally, monitoring occupation in terms of cancer incidence will permit earlier detection of potential hazards than could be achieved by mortality studies.

PUBLICATIONS: None to date
Leukemia Risk in Linemen

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Recent reports have suggested that persons who are exposed to electric and magnetic fields either occupationally or by living near power lines are at increased risk of leukemia, particularly acute myeloid leukemia. This study is an epidemiologic case-control investigation of the risk of acute myeloid leukemia in telephone linemen, a group of workers exposed to power distribution lines and identified as being at risk in the work of other investigators. Through an arrangement with the Medical Research Department at American Telephone and Telegraph, we have identified all deaths from acute myeloid leukemia that occurred in active or retired telephone company employees between 1975 and 1980 from their computerized mortality data base. The death certificate diagnosis of these cases is being validated through a review of company medical records. A matched control group is being selected from the Bell System personnel data base comparable to the cases in age, sex, race, and calendar time of employment. Complete work histories for the study subjects will be obtained from the telephone company personnel service record cards. Onsite visits are being conducted to ascertain exact job titles and describe the job activities associated with line work and exposure to electric and magnetic fields. Actual field measurements using available meters are planned. Telephone company jobs will then be classified by degree of exposure to electric and magnetic fields. In the analysis we will determine the odds ratio of having ever been a lineman among the acute myeloid leukemia patients compared to the controls, and the degree of association of disease with field exposure.

Publications: None to date
TITLE

Genetic Predisposition to Workplace Myelotoxin

PRINCIPAL INVESTIGATOR

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SUMMARY

This project has been designed to test the hypothesis that there exists employees in the workplace who are genetically predisposed to the myelotoxic effects of polycyclic aromatic hydrocarbons. Testing will be accomplished by examining the effects of benzo-(a)pyrene, (BP), an ubiquitous pollutant, in two genetically defined mice strains, the C57BL/6 (B6) and DBA/2 (D2). The carcinogen will be administered intragastrically, and its immunosuppressive effects evaluated by a determination of the Natural Killer (NK) and bone marrow NK stem and stromal cell activities at 4, 8, and 12 weeks of age. Since NK activity has been shown to be predetermined by the genetic make-up and speculated as the first line of defense in the immunosurveillance against cancer, the results gathered in this study are expected to provide information regarding possible genetic predisposition to myelotoxic effects of chemicals in the working environment. Evaluation of the bone marrow NK stromal and stem cell activities will be accomplished by fibroblast colony formation (Marrow Stromal Cell Assay) and the ability for bone marrow reconstitution of NK activity in X-irradiated syngeneic mice. The results from these particular studies will aid in the mechanistic interpretation for the cellular changes observed in the genetically defined animals. While the pathogenesis for human cancer has yet to be completely understood, increasing information is now becoming available to suggest that there are employees who may be genetically predisposed to the myelotoxic effects of polyaromatic hydrocarbons. The results derived from this proposed project will be expected to aid in our understanding of what influence such predisposition may have upon the possible workplace related carcinogenesis.

PUBLICATIONS: None to date
Metabolic Activation of 7H-Dibenzo (C,G) Carbazole

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The n-heterocyclic polynuclear aromatic compounds are significant components of occupational and environmental contaminants such as coal tar, coke oven effluents, coal and oil shale processing effluents, automobile exhaust, and tobacco smoke. Members of the n-heterocyclic compounds have been shown to be potent carcinogens in many species, including the rat. Very little is known about the metabolism or mechanism of action of these carcinogens in mammalian systems because most of the previous metabolism studies have focused on the polycyclic aromatic hydrocarbon analogs, such as benzo (a) pyrene.

The objective of this proposal is to investigate the metabolism and the pathways of metabolic activation of the model n-heterocyclic compound 7H-Dibenzo (c,g) carbazole (DBC) in the whole cell system of rat liver cell cultures. Identification of major metabolites will be accomplished by chemical analyses of DBC metabolism products isolated from rat liver cell culture media and by comparison of the products to standards obtained by chemical synthesis. Proposals for the pathways of activation will be generated by determining the mutagenic potential of the major metabolites in a whole cell system, testing the hypothesis that the nitrogen atom in the ring is involved in the metabolism of DBC leading to interaction with genetic material. A system for measuring unscheduled DNA synthesis in rat liver cell cultures will also be developed and used to test the hypothesis.

In order to determine the role of n-heterocyclic polynuclear aromatics in occupational and environmental cancer, knowledge of the metabolism and disposition of the compounds in mammalian systems is necessary. The rat liver cell culture system is an ideal model for investigations of the metabolism, mutagenicity, and genotoxicity of this class of compounds. These studies will lead directly to hypotheses of the pathways of activation for DBC specifically and the n-heterocyclic compounds in general.

PUBLICATIONS: None to date
Environmental Chemicals and Eukaryotic Protein Synthesis

PRINCIPAL INVESTIGATOR

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SUMMARY

The long term goal of the research proposal is to elucidate the mechanism(s) of translational control as effected by chemical environmental contaminants which may interfere with normal hematopoietic functions (e.g., benzene, gold, and other heavy metals). Our specific objectives for this two-year project will be to: (1) Study the effect of benzene on the specific phosphorylation of eIF-2a in rabbit reticulocytes, (2) Purify the benzene-activated translational inhibitor(s) from rabbit reticulocytes, and (3) Study the mode of action of the purified benzene-activated translational inhibitor(s).

Methods to be used for this study will include: (1) protein synthesis assays, (2) analysis of eIF-2a phosphorylation by two dimensional SDS gel electrophoresis, and (3) purification of benzene-activated translational inhibitor(s) by column chromatography.

PUBLICATIONS: None to date
TITLE

Prostaglandin Synthetase and Lung Toxicity with BHT

PRINCIPAL INVESTIGATOR

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SUMMARY

Prostaglandin synthetase (PGS), an enzyme present in many mammalian cell types, has recently been shown to oxidize xenobiotic compounds to toxic and mutagenic metabolites in much the same manner as the more well known cytochrome P-450 system. Since the distribution of PGS in body tissues is different from that of cytochrome P-450, the metabolic activation of xenobiotics by PGS may explain some of the toxic and carcinogenic effects of compounds in tissues that have little or no cytochrome P-450. In this connection, it has recently been shown that butylated hydroxytoluene (BHT), a phenolic food additive antioxidant consumed in significant quantities by humans, causes toxic necrosis of Type I alveolar cells in lungs of mice. Furthermore, BHT also acts as a tumor promoter when given in conjunction with several known carcinogens in mouse lung. It is our hypothesis that BHT is converted to reactive products by the PGS present in the lung. In turn, these reactive metabolites of BHT are capable of causing these harmful effects in the lung.

Thus, this proposal seeks to demonstrate that BHT can be metabolized to reactive mutagenic products by the PGS present in lung tissues. Such a reaction may be responsible for the observed pulmonary toxicity of BHT in mice and potentially in humans. Thus, the implications of this study would include; (1) The ingestion of large quantities of BHT and related phenolic food antioxidants by consumers or the exposure of workers to high doses of BHT might lead to an increased risk of alveolar Type I cell toxicity, (2) Since hyperoxia increases the activity of PGS, patients requiring such therapy are particularly susceptible to the BHT-oxygen toxicity, and (3) Other tissues or cell types with a high content of PGS might also be susceptible to BHT toxicity. These include the reproductive organs (i.e. uterus), the macrophages, and other cells of the immune system.

PUBLICATIONS: None to date
PROGRAM AREA: Occupational Cancers
GRANT NUMBER: 1 R13 OH02086-01
AWARD PERIOD: 04/01/84 – 11/30/84
FY84 FUNDING: $10,000
CUM. FUNDING: $10,000

TITLE

Silica, Silicosis, and Cancer: An International Symposium

PRINCIPAL INVESTIGATOR

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SUMMARY

The University of North Carolina at Chapel Hill and the Society for Occupational and Environmental Health jointly sponsored an international symposium entitled "Silica, Silicosis, and Cancer". The Symposium was held April 3-5, 1984, in Chapel Hill, North Carolina.

The rationale for convening this symposium is that there is now evidence that silica may act as a carcinogen. Silica has heretofore been considered a fibrogenic dust that causes silicosis, the sequelae of silicosis, and an old occupational disease whose incidence is declining. If silica may be a carcinogen (alone or combined with other hazardous materials), the concern is that there is a range of between 520,000 and 3,200,000 workers potentially exposed. Some of the occupations include auto workers, cement workers, ceramic workers, construction workers, foundrymen, glass makers, granite workers, metal ore miners, masons, quarrymen, sandblasters, silica brick workers, and tunnel builders.

Recent experimental animal evidence suggest that silica alone produces pulmonary histiocytic lymphomas and lung tumors. These experimental results support the findings of lung and gastrointestinal cancer excesses observed among workers who it is assumed were highly exposed to silica and other particulates. Despite the general lack of industrial hygiene measurements to confirm the effect of silica exposure, lung cancer excesses have been reported for the following occupations: gold and metal ore miners, foundry workers, sandblasters, silica firebrick makers, ceramicists, and granite workers. Miners, foundrymen, and granite workers also have elevated risks for gastrointestinal cancers. Of special note are the striking relative risks between three and six for lung cancer in two followup studies of silicotics in Sweden and Canada. Swedish researchers have recently confirmed their initial result with a new case-control study of lung cancer among silicotics.

Leading researchers in this field addressed the Symposium. In addition, presentations of new findings were made. We anticipate that the Symposium and publication of the proceedings will permit scientists in this wide field to share common intellectual ground, thus permitting new research endeavors to be undertaken.

PUBLICATIONS: None to date
TITLE
Explosion Hazards Related to Grain and Feed Dusts

PRINCIPAL INVESTIGATOR
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SUMMARY
A strong motivation behind the inception of this research program has been the continuing incidences of dust explosions in grain elevators, feed mills and flour mills. Similar disastrous events occur in coal mines, coal pulverizers, the pharmaceutical industry, etc. As compared to gaseous and liquid fuels, relatively little is known about the ignition, combustion, and explosion of dusts. This program is directed to the generation of the fundamental data and understanding so that the application of such knowledge could serve to prevent dust explosions or to minimize the damage if an explosion should occur. Two unique facilities have been developed for these studies, a Flame Acceleration Tube and a Premixed Turbulent Combustion Bomb. These facilities allow for the study of many dusts and the capability of controlling the test conditions and test variables of perceived interest. The important aspect of fluid mechanics is also included. An interactive experimental-theoretical approach is being used and proposed. At this time the emphasis is on grain dusts but the techniques developed should be applied to other dusts and powders in the future.

PUBLICATIONS
Kauffman CW: Agricultural dust explosions in grain handling facilities. SM Study #16, University of Waterloo Press, 1982

Kauffman CW and Nicholls JA: Dust explosion research at The University of Michigan. SM Study #16, University of Waterloo Press, 1982
Feedback and Safety: Involving Workers

PRINCIPAL INVESTIGATOR

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SUMMARY

The delivery of reinforcing and corrective feedback following the safe or unsafe performance of workers in occupational settings has repeatedly demonstrated its promise as a method for reducing or preventing accidents or their precursors. Much, however, remains to be discovered about the optimal use of feedback. Among the relatively unexplored variables in this domain is to what extent involving the direct participation of workers as a source of delivery of feedback will influence safe performance on the job. Related findings from studies of workers' involvement in goal selection and other aspects of organizational policy and practice have yielded promising results. In the proposed study the main purpose, consequently, will be to examine the extent to which involving workers in the safety program by having them serve as the source of (primarily positive) feedback will enhance safe performance on the job. Specifically, we plan to assess safe job performance, train volunteer workers to supply performance feedback, and compare the results against the feedback practice currently in effect. It is hypothesized that such worker involvement will enhance or sustain high levels of safe job performance, reduce accidents, and increase satisfaction with the program.

PUBLICATIONS: None to date
PROGRAM AREA: Traumatic Injuries
GRANT NUMBER: 1 R03 OH01687-01
AWARD PERIOD: 08/01/83 - 07/31/84
FY83 FUNDING: $ 22,910
CUM. FUNDING: $ 22,910

TITLE

Occupational Hazards to Health Sciences Employees

PRINCIPAL INVESTIGATOR

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SUMMARY

Hazards to employees of health care settings noted in the literature are numerous and varied. The literature is filled with reports of job-related hazards; however, reports of studies quantifying risks of identified threats to some population are very limited. The health services industry is the third largest employer in the U.S. with about five million workers.

This study will examine the problems of occupational hazards at a midwestern major state university health sciences teaching center and hospital by reviewing all Supervisor's First Report of Occupational Injury and Illness cases reported for the last two fiscal years (n=2,000). Research objectives are: (1) to quantify attack rates of hazards cited as important in the literature; (2) to describe injury and illness distributions from FY 1982-1983; (3) to classify these injuries and illnesses according to job class, department, hazard category, age, sex, and time; (4) to identify employee groups with the five highest occurrences by job class, department, age, and sex; and (5) to identify specific groups of employees which warrant further research in (a) analytic epidemiology, and (b) planning occupational health services delivery programs to promote a safe and healthful working environment. Population risks will be assessed using general personnel employment figures for exposure group data.

Although extrapolation of findings to other settings will be limited to this setting, a method will be developed and tested to identify high risk job-classifications and departments. This will help to direct and justify further research efforts requiring more expensive and time consuming research designs and methodologies that can be used in other settings. The study will also attempt to determine the usefulness of first report of injury records as an epidemiologic tool in addition to describing job-related hazards to a specific population affected.

Another major product of this study will be data for internal planning. The principal investigator will provide pertinent data to department heads and work with them to develop occupational safety and health programs and services through the university.

PUBLICATIONS: None to date
PROGRAM AREA: Cardiovascular Diseases
GRANT NUMBER: 5 R01 OH00906-04
AWARD PERIOD: 08/01/82 - 07/31/84
FY83 FUNDING: $ 81,108
CUM. FUNDING: $444,505

TITLE

Job Conditions, Occupations, and Cardiovascular Disease

PRINCIPAL INVESTIGATOR

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SUMMARY

The object of this research is to examine U.S. data on cardiovascular disease and job conditions for associations similar to those recently obtained by these researchers in cross-sectional and prospective analysis of Swedish national data. Those findings confirmed the relationship between C.V.D. and psycho-social job characteristics using a previously untested model of job psychological strain development based on job decision latitude (low) and psychological job demands. These same job characteristics have been previously shown to be stress-related in both U.S. data and Swedish data based on comparable populations and survey instruments.

We propose to examine five major U.S. data bases including information on job characteristic and C.V.D. or C.H.D.: The H.I.S. (1972); H.E.S. (1960-62); H.A.N.E.S. (1970-75); the Western Collaborative Study; and the Framingham Study. While data measuring job characteristics is generally weak in all existing large scale U.S. C.V.D.-C.H.D. data bases, the above surveys do contain either limited direct measures of the relevant job characteristics or detailed U.S. Census Occupational Codes (382 categories). These codes can be used to indirectly assess job condition impacts with the help of job characteristic-occupation data in three national U.S. working condition surveys (1969, 1972, 1977). The U.S. data bases also allow isolation of the unique contribution of job conditions to C.V.D. risk, through multivariate control for conventional risk factors (especially age, smoking, serum cholesterol, type A behavior and socio-economic status). It should be noted that our model, based on work environment conditions, represents an alternative psycho-social mechanism of disease development to that implied by current "Type A" behavior research (based on personality characteristics). Also, previous U.S. and Swedish findings based on the model have not substantially weakened when socio-economic status is controlled.

The presently available U.S. data probably cannot provide the final assessment of job-related C.H.D. risk. Our proposal makes maximum use of the extensive existing data resources, and should provide a basis for development of more exact data collection instruments in the future. Our project output will include a recommended job analysis instrument, as well as discussion of detailed occupational categories presently at risk in the U.S.
PUBLICATIONS

PROGRAM AREA: Cardiovascular Diseases
GRANT NUMBER: 1 K01 OH00011-01
AWARD PERIOD: 09/28/84 - 08/31/86
FY84 FUNDING: $32,400
CUM. FUNDING: $32,400

TITLE

Lead Burdens, Exposure Estimates and Hypertension

PRINCIPAL INVESTIGATOR

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SUMMARY

There are two major objectives addressed in this proposal. The first is to develop epidemiologically useful tools for estimating cumulative lead exposure and to conduct a pilot case-control study investigating a potential relationship between lead and hypertension.

A detailed environmental and occupational lead exposure questionnaire will be administered to a sample of hypertensives who have been subjects of a prior study to confirm the correlation between X-ray fluorescence measurement of lead stores in bone and urinary lead excretion following diagnostic chelation. X-ray fluorescence values will be available for thirty patients and chelation values for approximately fifteen in this group. The predictive value of component questions and of a variety of dichotomous scoring techniques will be determined, using first diagnostic chelation results then X-ray fluorescence results to establish validity. Reliability will be established through repeated questionnaire administration. X-ray fluorescence will be performed on thirty non-hypertensive orthopedic clinic patients who will be selected as age, sex, and race matched controls. The specificity and sensitivity of the exposure questionnaire will be confirmed in this group. A case-control pilot study comparing both lead exposure estimates and X-ray fluorescence values among hypertensives and non-hypertensive orthopedic patients will be performed. This pilot is not intended to produce definitive results but rather to refine study instruments, evaluate adequacy of matching and determine the sample size needed for a future study. It is a necessary first step which would then allow the question of whether hypertensives have elevated body burdens of lead to be addressed and, if so, whether this is predictable in a given individual on the basis of history. A future question of potential widespread health impact is whether therapeutic chelation in hypertensives with increased lead burdens would affect blood pressure control.

PUBLICATIONS: None to date
A Statistical Method for Detection of Work-Related ASCVD

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This proposal is designed to address methodological issues believed to be important in epidemiologic studies of the role of occupation in the development of cardiovascular disease mortality. Since arteriosclerotic cardiovascular disease (ASCVD) accounts for approximately 35-40% of all deaths in the U.S.A., occupational exposures that are associated with relative risk (RR) of 1.3 for ASCVD are as important to detect and control from a public health point of view (measured in terms of excess deaths) as an exposure associated with a RR of 12 for cancer (e.g. bladder cancer) that accounts for less than 1% of all deaths in the U.S.A.

Since the incidence of ASCVD is great, most large retrospective cohort studies have the power to detect a RR of 1.3. Thus the failure to detect important (RR - 1.3) occupational causes of ASCVD should not be a problem of power (sample size).

Review of the epidemiological methods used to study mortalities suggest that few occupational causes of cardiovascular disease have been identified, in part, because of inappropriate comparisons of working populations with the general population. Recently, intracohort analyses that compare workers in different exposure categories within a single industry have been undertaken in an effort to develop a method which would properly estimate occupationally related risk of death from ASCVD. Unfortunately, as Gilbert has shown, the available statistical methods for intracohort analyses still tend to underestimate the effect of cumulative exposure. This underestimation results from utilizing date of death as the sole outcome variable. As a consequence, intracohort analyses may, also, fail to detect work-related disease when present. In this proposal a methodology is presented which, by utilizing date of termination of employment in addition to the date of death as an outcome variable, produces an unbiased estimate of effect of cumulative exposure. The accuracy of estimates obtained with the new method will be compared to those obtained with standard methods in computer simulations. Finally, mortality data from a large rubber worker cohort will be reanalyzed both with the new method and standard methods and the results compared. If the new method proves as useful as theoretical consideration would suggest, it should provide an improved means for detecting causes of chronic disabling diseases.

PUBLICATIONS: None to date
TITLE

Heart Disease in Metalworkers: Occupational Determinants

PRINCIPAL INVESTIGATOR

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SUMMARY

This proposal will investigate the etiological relationship of noise, heat, and other hazards in the work environment to cardiovascular disease and overall physical health status.

The data used will be from the METELLI project, a prospective ten-year study on metalworkers in Finland that has collected information in exposures to specific hazards, job characteristics, psychosocial functioning, and medically-determined health status.

Independent variables of interest to this study include industrial hygiene measurements of noise, heat, silica, and light; job characteristics such as work pace, monotony; psychosocial functioning such as social support, stress symptoms; and health practices such as smoking and alcohol consumption, diet.

Outcome measures will include cardiovascular disease morbidity and mortality and overall morbidity and mortality.

Results will provide evidence on the individual and joint effects of the independent variables on worker health, with particular attention to cardiovascular disease.

PUBLICATIONS: None to date
PROGRAM AREA: Reproductive Disorders
GRANT NUMBER: 5 R01 OH00835-06
AWARD PERIOD: 09/29/82 - 08/31/85
FY84 FUNDING: $ 48,090
CUM. FUNDING: $219,469

TITLE
Occupational Risks of Pesticide Exposure for Females

PRINCIPAL INVESTIGATOR
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SUMMARY

The proposed study is designed to characterize some of the reproductive hazards that confront females engaged in occupations which subject them to potential exposure to pesticides. This study will critically evaluate the effects of pesticide exposure on specific essential functions of the female reproductive system. The pesticides employed in this study represent the three major groups of such agents. These pesticides are DDT, malathion, kepone, and carbaryl. Specific aims of this investigation are to ascertain whether the effects of pesticide exposure on the female reproductive system are a function of age of the exposed individuals and whether age is a factor in determining the exposed individuals ability to return to normal reproductive activity. Groups of immature mice (20 days old), young sexually mature mice (7-11 weeks), mid-sexually mature mice (6-8 months), and late sexually mature mice (10-12 months) are to be subjected to acute pesticide exposure (5 consecutive days) or longer term exposure (5 consecutive days during four consecutive weeks). After pesticide exposure, the reproductive system will be examined to assess the effects of these pesticides on various reproductive parameters. These include gas chromatographic analysis of pesticide levels in the liver, changes in the number of different classes of follicles in the ovary, numbers of oocytes ovulated and the distribution of the steriodogenic enzyme, \( \Delta^5 \) -3\( \beta \)-hydroxysteroid dehydrogenase and acid and alkaline phosphatase activity within the different compartments of the ovary. This study is nearly completed and we are presently in the midst of assessing the reversibility of pesticide-induced effects on the female reproductive system once exposure to the pesticide ceases. A return to normal reproductive activity will continue to be evaluated in the coming year by assessing biological activities and cytological appearances of the different cellular components of the ovary and by determining the mating ability and fertility of these individuals previously exposed to pesticides. Another aim of this study is to make inroads into assessing the roles of combination of pesticides in modifying the effects of a single pesticide. Reproductive parameters will be examined only in female sexually mature mice exposed to combinations of either Kepone and carbaryl or Kepone and malathion. Information obtained from all the above-mentioned studies will serve to assist both employer and employee in properly evaluating what role a female should have in occupations in which pesticide exposure is a reality.
PUBLICATIONS


Swartz WJ: Ovulatory response of mature mice to exogenous gonadotropins following acute exposure to DDT. Anat Rec 205:195A, 1983


TITLE

Occupational Hazards to Male and Female Fertility

PRINCIPAL INVESTIGATOR

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SUMMARY

The objective of this multidisciplinary project is to establish a set of innovative, sensitive and practical tests of reproductive functions in men and women, and to demonstrate their application in the field of occupational safety and health. In men these tests will assess the physiological functions and fertility of spermatozoa, and will thus be able to detect very early testicular damage resulting from exposure to environmental hazards. The tests focus on sperm morphology in semen, sperm motility in semen and cervical mucus, and the ability of sperm to penetrate non-living, immature human oocytes and zona pellucida-free hamster eggs. This multiphasic approach to detection of early warning signs of reproductive toxicity is pioneering, and has never been applied in the field of occupational safety and health. In women the tests will detect occult pregnancy and predict whether spontaneous abortion is likely to occur. The tests focus on the changing levels of hCG in urine during the first two weeks of pregnancy, and their application to occupational medicine is also without precedent. The implementation of this project is in two basic phases. During the first two years, our expertise in human reproductive physiology will be applied to simplify the new tests and select the most sensitive and practical for application in the field. During the second two years, our resources in epidemiology and community medicine will be used to demonstrate application of the selected tests in several different populations of male and female workers exposed to different occupational health hazards.

PUBLICATIONS: None to date
Spermatogenic Transfer of the Effects of Mutagens

**PRINCIPAL INVESTIGATOR**

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**SUMMARY**

There is considerable concern about identifying the potential risks for individuals who work in occupational settings requiring frequent exposure to chemicals which may have mutagenic or carcinogenic potential. While women of child-bearing age are frequently not permitted to work in these high risk settings, men are not so protected. The teratological effects of in utero exposure to toxic agents is fairly well studied but the potential mutagenic effects on the male have just begun to be appreciated. We propose to examine the mutagenic effects of a number of chemicals which are felt to present significant risks to man. Our approach is to utilize a rodent model to examine the spermatogenic transfer resulting from the treatment of the male parent with selected mutagens to the F1 progeny. Our studies include the examination of behavioral development in the progeny, cytogenetic studies for chromosomal abnormalities and neuroanatomical and neurochemical examination of the brains of the progeny. In addition, we will examine mid-gestation embryos in order to determine pre- and post-implantation mortality and embryonic chromosomal characteristics. We plan to breed a portion of the F1 progeny and determine if evidence of behavioral teratogenesis, cytogenetic anomalies or neurochemical alterations exist in the F2 generations as a result of mutagen exposure.

**PUBLICATIONS**

Adams PM, Fabricant JD, and Legator M: Effect of paternal cyclophosphamide exposure on F1 progeny active avoidance behavior. Neurobehavioral Toxicology and Teratology 4:531-534, 1982


TITLE

Effects of Carbon Disulfide on Male Reproduction

PRINCIPAL INVESTIGATOR

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SUMMARY

Neurological, behavioral, vascular, coronary, as well as reproductive and endocrine lesions, have been found in humans and laboratory animals exposed to carbon disulfide (CS$_2$). Of particular concern is the fact that these effects occur in workers exposed to $\pm$ 20 ppm of CS$_2$, the current Federal exposure limit. The potential adverse pregnancy outcome in wives of CS$_2$-exposed workers has not been examined, and is the topic of the proposed research. That spermatotoxicity can be associated with adverse pregnancy outcome has been documented for a variety of drugs and environmental agents.

We propose to employ a new animal methodology and protocol to determine: 1) the level of CS$_2$ exposure associated with reproductive toxicity, and 2) whether such toxicity is associated with adverse pregnancy outcome as reflected in teratologic or postnatal neurobehavioral evaluation. To this end, the proposal is divided into 3 phases incorporating areas of reproductive physiology, endocrinology, histopathology, teratology, and neurobehavioral toxicology.

In phase I groups, of 60 male rats will be exposed by inhalation to 300, 100, or 10 ppm of CS$_2$ for 70 days. Spermatogenic (sperm count, motility and morphology, testicular histology) and endocrine (FSH, LH and testosterone) profiles will be obtained at 1, 4, 7, and 10 weeks of exposure. Data from these investigations will allow for selection of appropriate dose and duration of exposure to be more extensively studied in phase II. This second series of investigations will be unique to animal model studies, in that a "within-subjects" design will be utilized. Procedures have been developed that allow for repeated collection of semen and serum samples from each animal during CS$_2$ exposure that may be compared to its pre-exposure baseline values. In addition, measures of coital behavior and neurobehavioral status of the male will be obtained. Moreover, near the end of exposure, each male will be mated to two females. One female will be sacrificed (Day 21 of gestation) for teratologic evaluation. The second female will be allowed to deliver with neurobehavioral assessments conducted on the progeny. The final phase proposed will employ a "within-subjects" design to examine the time course for recovery following termination of CS$_2$ exposure.
PUBLICATIONS


PROGRAM AREA: Reproductive Disorders
GRANT NUMBER: 5 RO1 OH01281-03
AWARD PERIOD: 09/29/82 - 08/31/85
FY84 FUNDING: $114,466
CUM. FUNDING: $309,960

TITLE
Embryo Culture/Teratogen Biotransformation System

PRINCIPAL INVESTIGATOR
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SUMMARY

Specific Aims:

1. Enzyme inducing agents, including phenobarbital, 3-methylcholanthrene, polychlorinated biphenyls, ethanol (and others, if time permits) will be employed to investigate the qualitative and quantitative effects of changes in enzyme complement on malformations elicited in the embryo culture systems. These inducing agents will be studied in Sprague-Dawley Rats during the earlier stages of gestation and effects as various xenobiotic biotransforming systems will be assessed to better determine what relationships exist between metabolic activities and incidence and type of observed malformations. The relative effects of tissue homogenates, slices, various homogenate subfractions and fine tissue fragments can help us to better evaluate the contribution of the various participating enzymes.

2. In cases in which bioactivation of proteratogens has been established in the embryo culture system (e.g. with 2-acetylamino-fluorene), attempts will be made to identify proximate and ultimate teratogenic species. A number of approaches will be utilized in attempts to accomplish this goal. Suspect metabolites can be added directly to the embryo culture system; selective inhibitors and activators of specific metabolic pathways can be used to corroborate other evidence; free radical scavengers, antioxidants, inhibitors of lipid peroxidation, etc. may also be found useful in determining not only which metabolite or metabolites may be acting as proximate or ultimate teratogens in vitro, but also through what mechanisms the reactive intermediates may be eliciting the malformations.

3. A continuation of investigations of the participation of xenobiotic conjugating enzymes as participants in and determinants of the elicitation of malformations in embryo culture systems by foreign organic chemicals. These aspects can be studied in conjunction with purified enzymes which catalyze the breakdown of such conjugates—e.g. sulfatase, E-glucuronidase, etc.

4. Cocultured human tissues, including liver, adrenal glands, placentas, and fetal tissues will be used as enzyme sources in investigations of the influence of biotransformation on teratogenicity in vitro.
PUBLICATIONS


TITLE

Occupational Exposure of Parents and Tumors in Offspring

PRINCIPAL INVESTIGATOR

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SUMMARY

The objective of this proposed study is to determine the extent to which occupational exposures to parents account for tumors in offspring. We proposed to study the relationship between parental occupational exposure and common childhood cancers by the case/control approach. Children less than 15 years of age will be studied.

Cases of childhood cancers will be identified by the University of Southern California Los Angeles County Cancer Surveillance Program (CSP), a comprehensive population based tumor registry covering more than 7 million people. In children under 15 there are approximately 225 new cases of cancer in Los Angeles County each year about equally divided by the sexes. Over a five year period, the CSP should yield approximately the following number of childhood cancers: 325 leukemias, 200 brain tumors, 55 kidney tumors, 60 bone tumors, and 75 connective tissue tumors. These cases will be the subject of our study.

Neighborhood controls will be selected by an established algorithm. Parents of cases and controls will be interviewed by a standardized questionnaire to ascertain complete occupational histories for both parents. Information concerning other exposures of etiologic significance and potential confounding variables will also be collected (age, race, socioeconomic status, tobacco use, drug use, exposure to ionizing radiation, family history of malignancy and congenital malformation, non-occupational exposures, etc.).

The collected information on occupation will be reduced to specific chemical exposures wherever possible and relative risks will be determined for the various occupations and exposures. In addition, we will examine the importance of timing of exposure (prior to, during, or after pregnancy), breast feeding, and the relative effects of exposure to mother or father.

Identification of occupations or exposures that result in increased risk has important public health implications.

PUBLICATIONS: None to date
The Role of Hyperthermia in Congenital Malformations

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SUMMARY

We believe that maternal hyperthermia during the critical stages of embryogenesis may act synergistically to enhance the teratogenic effect of threshold or sub-teratogenic levels of known teratogenic agents. In our animal model, we have shown that short-term maternal environmental hyperthermia enhances the teratogenic effect of vitamin A, the metal indium, and the metalloid arsenic. We plan now to extend these observations to study in depth the relationship of maternal hyperthermia, to the specific malformations caused by 5 different heavy metals: cadmium, lead, arsenic, indium, and mercury. It is our opinion that the combination of hyperthermia and heavy metals are ideal tools to use for this study. Environmental hyperthermia is an easily controlled laboratory procedure and exposure of pregnant animals to short term hyperthermia produces specific patterns of central nervous system defects in our animal model. The same animal model, used for teratogenic studies with the heavy metals mentioned, produces a specific and different pattern of developmental malformations for each metal.

The specific aims of this proposal are: first, to determine whether or not there is any synergistic teratogenic interaction between maternal hyperthermia and cadmium, mercury, or lead. In addition, we will study the effect of hyperthermia on the caudal dysplasia syndrome which is so effectively induced by simultaneous exposure to lead and cadmium. We will also examine the effect of hyperthermia on the marked protective effect that zinc has on the teratogenic activity of cadmium. Secondly, we will study the effect of chemical status of the 5 teratogenic metals in the materno-embryonic unit. A third study will consider the effect of maternal hyperthermia and these metals in combination on certain biochemical events in the materno-embryonic unit. Maternal hyperthermia may play a very significant role in the etiology of congenital malformations, not only because of its own inherent teratogenic potential, but also because of its possible interaction with other known teratogenic agents. We believe that the combined use of maternal hyperthermia and the heavy metals we have chosen, in a combined biochemical, teratological and histopathological approach, will give us reliable and substantial quantitative data to help explain these interactions.
PUBLICATIONS

Ferm VH and Hanlon DP: Constant rate exposure of pregnant hamsters to arsenate during early gestation. Environmental Research, (in press)


Reproduction Hazards of Dinitrotoluene Toluyenediamine

PRINCIPAL INVESTIGATOR

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SUMMARY

The compounds 2,4-dinitrotoluene (2,4-DNT) and 2, 4-toluyenediamine (2,4-TDA) are used widely, in the manufacture of polyurethane foams and industrial dyes. DNT is also used in the production of explosive, propellants, and in the synthesis of TDA. Evidence exists that 1) DNT is responsible for decreased spermatozoa, testicular atrophy, and epididymal degeneration in rodents and 2) TDA an in vivo metabolite in the male rat as well as a synthetic reduction product of DNT may be mutagenic. Preliminary studies carried out in our laboratories indicated that TDA exposure in male rats (at a dose comparable with 2,4-DNT may result in decreased fertility and reduce fetal viability. The sites(s) and mode(s) of action of these agents on the reproductive processes in the male rat are unknown. Increased circulating LH and testosterone levels appear to be related to the adverse reproductive effects of TDA and DNT in rats. (Preliminary findings).

The present proposal aims to determine: 1) the effects of DNT on a) sperm number, b) weights of testes, seminal vesicles, epididymides, and prostate glands, c) cellular architecture of the seminiferous tubules, and d) serum testosterone, LH and FSH concentrations in the male rat, 2) the order in which each endpoint is acted upon by DNT, 3) the effects of TDA in the male rat on a) sperm number b) weights of testes, seminal vesicles, epididymides, and prostate glands, c) serum testosterone, LH and FSH concentrations d) integrity of the seminiferous tubules, and e) number of successful fertilizations with receptive females, and 4) the mutagenic and teratogenic effects in litters from male rats fed 2,4-TDA. The information derived from these studies is particularly important in view of the hitherto unknown reduced fertility effect of 2,4-TDA in rats and b) altered circulating LH and testosterone levels in male rats treated with DNT or TDA. The long range goals of this study are to improve 1) our understanding of the underlying factors responsible for impairment of reproductive function by DNT and TDA in the rat and 2) the ability to forecast the onset of germ cell damage by these agents. For example, if testicular or spermatozoa effects are secondary to alterations in LH, FSH, or testosterone levels, the measurement of these hormones may be of value in predicting reproductive
toxicity by DNT or TDA, and thereby avoid permanent gonadal lesions by continued exposure to these agents.

PUBLICATIONS: None to date
TITLE

Reproductive Effects of Leads or Solvent Exposure at Work

PRINCIPAL INVESTIGATOR

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SUMMARY

The aim of this study is to investigate, whether exposure to organic solvents or inorganic lead influences pregnancy outcome. The exposed group consist of women and men who, according to the biological monitoring data, have been exposed to organic solvents or lead through 1972 to 1982. It is estimated, that there would be 41-121 (minimal-maximal estimation) spontaneous abortions among the solvent exposed women, and 80 spontaneous abortions among the wives of the solvent exposed men. Among the lead exposed women the estimated number of spontaneous abortions is 22 and among the wives of the lead exposed men about 140 (minimal estimations). The cases of spontaneous abortions will be identified from the hospital discharge register maintained at the National Board of Health. A possible high risk for congenital malformations in the children of the exposed women can be excluded or confirmed by using the Finnish Register of Congenital Malformations. The figures will be compared with regional controls of a similar socioeconomic status. The anticipated result; the possible effects of organic solvents or lead at various exposure levels on the pregnancy outcome of the workers are of value in prevention of health hazards. They can also be helpful for the understanding of dose-effect relationships and for the planning of occupational hygienic standards.

PUBLICATIONS: None to date
TITLE

Role of Gap Junctions in Adverse Reproductive Outcome

PRINCIPAL INVESTIGATOR

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SUMMARY

Direct intercellular communication between adjoining cells can occur among cells in vitro and in vivo, most likely through specialized channels called gap junctions. It has been suggested that gap junctional communication plays an important role in embryonic development, germ cell maturation, and parturition. Our proposed research will investigate inhibition of junctional communication as a possible mechanism of adverse reproductive outcome, and will test the validity of several short-term assays for the detection of reproductive toxins that may act by this mechanism. The first part of our research program will entail testing known and potential reproductive toxins for their ability to interrupt junctional communication using rapid in vitro techniques. We will employ several different cell lines in an attempt to maximize the reliability of the in vitro systems as predictors for the human, in vivo situation. These cell lines will include Chinese hamster V79, human teratocarcinoma, human uterine, and rat hepatocyte lines. The second focus of our research will be to validate inhibition of junctional communication as a mechanism of abnormal morphogenesis using hydra reaggregation as an in vivo development system. By differentially labelling and later mixing and reaggregating two populations of hydra cells, we hope to demonstrate that compounds which interfere with hydra reaggregation also interrupt junctional communication in vivo. These results will be compared to the results from cell systems to determine the reliability of the cell systems in predicting developmental toxicity. Finally, we will investigate molecular mechanisms of gap junction function. We will focus our efforts on protein phosphorylation, since this has been associated with growth factors, receptor function, and junctional communication.

PUBLICATIONS: None to date
PROGRAM AREA: Reproductive Disorders
GRANT NUMBER: 1 K01 OH00035-01
AWARD PERIOD: 09/28/84 - 08/31/87
FY84 FUNDING: $ 32,152
CUM. FUNDING $ 32,152

TITLE

Genotoxic Exposure Assessment by Simplified DNA Analysis

PRINCIPAL INVESTIGATOR

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SUMMARY

The objective of this project is to use currently available molecular biological techniques to develop a sensitive and practical test of exposure to genotoxic agents. A set of enzymatic treatments of the human aliphoid DNA sequence will be tested in the laboratory for efficacy in detecting abnormalities induced in irradiating T-lymphocytes in freshly drawn blood. Primary emphasis will be placed on procedures which lead to the cleavage of aberrant DNA while leaving the normal 342 base pair aliphoid sequence intact. Preliminary experiments will employ P-32 labeled nucleotides and autoradiography of electrophoresis gels to assess cleavage rates. As the procedure is optimized, less energetic labels will be employed and cleavage rates will be determined by liquid scintillation counting of two portions of the electrophoresis gel. The utility of High Pressure Liquid Chromatography will be investigated as an alternative for electrophoresis in routine applications.

After the mechanics of the technique have been optimized, a limited number of observations will be made on (presumably) minimally exposed members of the general population in order to estimate the residual background damage rate as measured by the procedure. Additional measurements will be made on blood samples from individuals with documented elevated occupational or therapeutic radiation exposures. An analogous procedure for use in a suitable laboratory animal will be sought in order that in vivo animal experiments can be used to supplement in vitro exposure studies. The utility of the procedure for assessing exposure to a selected group of chemical genotoxins will then be evaluated.

PUBLICATIONS: None to date
Mechanisms of Action of 3 Toxins on Male Reproduction

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The primary function of male reproduction is to produce sperm for the propagation of the species. Regulation of this process is under the control of various hormonal agents released by the testes and the pituitary. Minor alterations in the concentrations of these humoral agents in the body lead to the disruption of spermatogenesis in both man and other mammals. In some instances, toxic environmental agents can also induce a disruption of spermatogenesis. The United States Environmental Protection Agency has commissioned three studies, two on known male reproductive toxins and one on a suspected male reproductive toxin, to establish the efficacy of a technique for estimating the potency of toxic agents on male reproduction. The technique consists of measuring the weights of the male reproductive organs, testicular sperm content, epididymal sperm content, sperm motility and morphology, following exposure of rats to different concentrations of a toxic substance for at least 6 cycles of the germinal epithelium. Determination of these parameters will certainly establish whether a toxin will have an effect on male reproduction, as well as yield an estimate of the toxin’s potency. However, additional parameters need to be monitored to gain insights into the mechanisms of action of these toxins so that appropriate measures may be taken to treat exposed individuals.

This proposal requests support for investigation of the mechanisms of action of 3 toxins on male reproduction through analysis of tissue samples generated in previous studies. The specific analyses to be done are: 1) serum levels of follicle stimulating hormone and luteinizing hormone; 2) serum levels of testosterone; 3) testicular capacity for testosterone secretion; 4) morphometric analysis of the testicular germinal epithelium. Determination of these parameters will establish whether the pituitary-testicular hormonal axis has been disrupted by the toxins, as well as the developmental stage of spermatogenesis that has been affected.
PROGRAM AREA: Reproductive Disorders
GRANT NUMBER: 5 R03 OH01705-02
AWARD PERIOD: 07/01/83 - 06/30/85
FY84 FUNDING: $ 18,644
CUM. FUNDING: $ 34,421

TITLE
Alcohol Alterations of Prenatal Workshop Carcinogenesis

PRINCIPAL INVESTIGATOR
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SUMMARY
Studies carried over the last few decades have demonstrated that the fetus is susceptible to the carcinogenic action of many of today's chemicals commonly found in the work environment. In addition, recent evidence has suggested that this harmful effect can be passed along to future unexposed generations. The objective of this proposal is to establish the sensitivity of the fetus to chemical carcinogens and whether the effects of alcohol consumption modifies this effect both in the immediate and future offspring. This project has thus been designed to test the hypothesis that in utero exposure to 1,2-dimethylhydrazine (DMH) results in carcinogenic information that is incorporated in the somatic and germ cells of both the immediate and future progeny; and that alcohol consumption during pregnancy alters the sensitivity of the fetus to the effects of this chemical carcinogen. Testing of this hypothesis will be accomplished by determining the specific antitumor cell-mediated immunity (CMI) in Fischer F344 inbred rats, brought about by exposure to DMH and alcohol. Pregnant rats will be administered a 5% alcohol solution on day 6 of gestation followed by a subcutaneous injection of varying doses of DMH (0.0001 to 0.1 mg/kg) on day 16 of gestation. Antitumor CMI measurements will be determined 60 days post-partum for the dams, F1, F2, and F3 generations. Sensitivity of the offspring to in utero exposure of DMH and alcohol will be delineated by calculations of an Alcohol Perinatal Sensitivity Factor (APSF) and a Fetal Workplace Risk Factor (FWRF). Work has already been completed on the effects of perinatal exposure to DMH in the first generation. These results have demonstrated a significant antitumor response in both sexes and a threshold level of 0.01 mg/kg, 10 times lower than adult exposure. Certainly, with the increasing numbers of women of child bearing age entering the industrial workforce, and the recent concern of alcohol consumption during pregnancy, it is of utmost importance that information be obtained on such health hazards. This proposal has been designed in an attempt to answer some of these questions by applying the bio-analytical techniques we have developed over the past years in our laboratory.

PUBLICATIONS: None to date
PROGRAM AREA: Reproductive Disorders
GRANT NUMBER: 5 RO3 OH01713-02
AWARD PERIOD: 07/01/83 - 06/30/85
FY84 FUNDING: $ 17,980
CUM. FUNDING: $ 36,951

TITLE

Effect of Benzene on Fetal Hematopoiesis

PRINCIPAL INVESTIGATOR

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SUMMARY

This proposal seeks to determine the effects of low level maternal inhalation exposure to benzene on fetal hematopoiesis using sensitive erythroid and granulocytic stem cell assays as well as the usual hematologic assays. Recent work in this laboratory has shown that exposure to 10 ppm benzene, the current TLV, affects committed erythroid stem cell proliferation. In the fetus hematopoietic stem cells are undergoing rapid cell division and the dividing blood cell pool is rapidly expanding during organogenesis. It is, therefore, likely that maternal exposure to even low levels of benzene would have a profound effect of fetal hematopoiesis.

Groups of pregnant mice will be exposed to 100 ppm, 30 ppm, and 10 ppm during days 6-16 of gestation. Blood cell parameters will be monitored on 16 day old fetuses, 2 day old neonates and 6 week old adults which are progeny of the exposed dams.

Specifically the following questions will be studied after maternal exposure to low concentrations of benzene vapor:
1. What is the nature of the dose/response on fetal and neonatal hematopoietic stem cells?
2. Do any disruptions in hematopoiesis persist into young adulthood?
3. Are there any differences in the hematotoxic response between male and female fetuses?
4. Is the switch of functional hematopoiesis from the liver to the spleen and bone marrow affected in late fetal and neonatal life?
5. Is the normal progression of hemoglobin synthesis from fetal to adult type affected?

The low level benzene exposure by inhalation should allow extrapolation of our findings to realistic human exposure conditions.

PUBLICATIONS: None to date
PROGRAM AREA: Reproductive Disorders
GRANT NUMBER: 1 R03 OH01818-01
AWARD PERIOD: 07/01/83 - 06/30/84
FY83 FUNDING: $ 25,149
CUM. FUNDING: $ 25,149

TITLE

Occupational Exposures and Female Secondary Infertility

PRINCIPAL INVESTIGATOR

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SUMMARY

This case control study is designed to investigate several risk factors for secondary infertility in women including occupational exposure. The cases will consist of new female patients attending the Yale New Haven Hospital Infertility Clinic and two private clinics during a 12 month period. Women who have had at least one pregnancy will be asked to participate (estimated N = 300). Two control groups will be used. The first will include women investigated for infertility who have had a pregnancy and are diagnosed normal with an infertile spouse (estimated N = 250). The second control group will be composed of pregnant women who have been interviewed in a previous study, (N = 260). The purpose of the study is to identify occupations or specific job exposures that may increase the risk for secondary infertility in women. Its long term objective is to generate hypotheses regarding specific occupational groups that may require more definitive study.

PUBLICATIONS: None to date
TITLE

Occupational Factors Associated with Biliary Atresia

PRINCIPAL INVESTIGATOR

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SUMMARY

This retrospective epidemiologic study will investigate the hypothesis that parental occupational factors are associated with occurrence of Congenital Biliary Atresia (BA). Preliminary observation has raised suspicion regarding association with parental occupation, especially selected chemical exposures. Occupational and selected environmental factors reported by parents for the 6 months-preconceptual period, gestational trimesters, and neonatal period will be compared for cases and controls. This anomaly leads to progressive post-natal cirrhosis and debilitation, with death by age four in at least 60% of victims, despite Kasai procedure surgery. Etiology is unknown and little studied epidemiologically due to previous insufficient aggregates of cases. Principal objective is to determine whether reported chemical or other occupational employment of parents constitutes a significant factor associated with BA occurrence, or a subgroup thereof. Additional aims include determination of:

1. Associated selected home or avocational exposures
2. Whether teratogenic associations are related to paternal or maternal exposure(s), or to specific combined exposures (interactions)
3. Increased incidence of other teratogenic outcomes (including spontaneous abortion) in case sibships (correlated with parental occupation for each pregnancy)
4. Associated familial occurrence of hepatitis (B and other), and other specific conditions
5. Maternal health status and perinatal complications
6. Selected demographic and socioeconomic variables

Consecutive cases (n=400), both living and deceased, from infancy to pre-school aged, will be obtained from the National BA Registry of the American Academy of Pediatrics. Regional, age, and time-matched controls will be selected from each respective case surgeon's files to provide approximate case control equivalence on temporal and geographic variables. Case diagnoses will be validated by review of selected medical reports. Data on outcome and potentially confounding variables will be obtained through an indepth interview with parents. Distribution and
cross-tabulations of various occupations, occupational groupings (based on similar chemical exposures), and other environmental factors will be done by case-control status, after adjustment for potential environmental, socioeconomic, and pre-perinatal confounders. Multiple regression analysis will be used to weight significant variables, identify significant interactions, and adjust for confounding variables.

PUBLICATIONS: None to date
TITLE
Relation of Seminal Metabolites to Reproductive Insult

PRINCIPAL INVESTIGATOR
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SUMMARY
The purpose of this proposal is to try to establish a relationship between concentrations of one of two compounds, known to have effects on the male reproductive system, and their metabolites in the seminal compartments (seminal plasma and germ cell) with indices of spermatotoxicity (sperm count, motility, viability, morphometry, and morphology). Additionally, it will be determined if threshold concentrations of the xenobiotic can be identified for the affected spermatogenic parameters, how recovery is related to different dosages, and how these two compounds, representing two different chemical classes, differ in their distribution, effects, and ability to predict risk from their seminal concentrations. The compounds chosen for study are ethylene dibromide and 2-ethoxyethanol. All experiments will be performed on adult, male rabbits. There will be three phases to this study along with the development of the analytical techniques. The analytical technique employed will be GC. The first phase will determine a rough time course for each compound in the semen. The second phase will be used to identify the actual metabolites in the seminal compartments, and to more accurately determine the kinetics in the blood and semen. This project is important as concern for male reproductive toxicity is growing. Moreover, this approach is noninvasive and may be applicable in the human population.

PUBLICATIONS: None to date
TITLE

Toxicology of Industrial Chemicals Acting on the CNS

PRINCIPAL INVESTIGATOR

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SUMMARY

The experimental part (90%) of this study will examine the known
neurotoxicity and the possible neuroteratogenicity of the vinyl monomer
acrylamide and the ketonic solvent 2, 5-hexanedione (the primary toxic
metabolite of the hexacarbon solvents n-hexane and methyl n-butyl_ketone).
These compounds are widely used in commercially important polymers and
solvents, but their neurotoxic properties make them significant industrial
chemical hazards and environmental pollutants. Previous experimental studies
with these chemicals, in which we demonstrated their ability to produce
central-peripheral distal axonopathy, will be extended to examine by light
and electron microscopy: 1) the brain damage produced by chronic low-level
systemic intoxication; 2) the extent and reversibility of nervous system
damage after chronic exposure to these neurotoxins; 3) the differential
effects of acute and chronic intoxication on the axon and supporting cells
(Schwann cell, oligodendrocyte and astrocyte) in fetal, post-natal, adult,
and aged states. These data will bear heavily on our understanding of the
site of action of these agents and why the distal parts of central and
peripheral nerve fibers are vulnerable to systemic intoxication. Light and
electron microscopy will also be employed to study any abnormalities in the
nervous system of fetal and post-natal rats which have been exposed to
acrylamide or to 2, 5-hexanedione in utero. The clinical part (10%) of this
study will develop and evaluate a simple assay of palmar vibration
sensibility presently being used in acrylamide manufacturing plants for the
detection of early, sub-clinical neurological damage in potentially exposed
workers.

The objectives of these studies are 1) to meet some of the Research
needs specified in National Institute for Occupational Safety and Health
Criteria Documents for Acrylamide (1976) and Alkanes (1977) and elsewhere in
U.S. Environment Protection Agency reports on Acrylamide (1976, 1977) and
Diketone Solvents (1977), 2) to develop new, sensitive methods for the
assessment of chemically induced neurotoxicity and neuroteratogenicity, and
3) to illuminate the mechanism of neurotoxin-induced nerve fiber degeneration.
PUBLICATIONS

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Neurology 15:313–315, 1984

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experimental studies of 2-t-butylazo-2-hydroxy-5-methylhexane neurotoxicity.
Annals of Neurology, in press
TITLE

Occupational Neuropathies Due to Industrial Chemicals

PRINCIPAL INVESTIGATOR

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SUMMARY

Humans are exposed to many chemicals, some of which may cause damage to the nervous system. Cases of outbreak of occupational neuropathies are well-documented. Among these chemicals are the industrial solvents n-hexane and methyl n-butyl ketone as well as organophosphorus pesticides. Neurotoxicity of compounds belonging to these two classes of chemicals have been studied in different experimental animals. Although the rat has low sensitivity to MnBK, it has been the animal most used in studying hexacarbon neurotoxicity. On the other hand, the chicken has been the animal of choice to study organophosphorus-induced delayed neurotoxicity. Because humans are often exposed simultaneously to chemicals from both of these groups, it is important to study their neurotoxic effects in the same experimental animal, so that assessments can be made regarding the risk of human exposure to these chemicals. During the first phase of this study, we have been investigating the interaction between neurotoxicity induced by hexacarbons, carbon solvents, and organophosphorus esters in the chicken, that is sensitive to neurotoxicity produced by both classes of neurotoxicants. We propose to continue our studies of the effect of exposure to multiple chemicals on the developing of neurotoxicity in hens. We propose to study the interaction between neurotoxicity induced by n hexane or its related chemicals, MnBK, methyl iso-butyl ketone, (MiBK), 2, 5-hexanediol (2,5-HDOH), or 2, 5-hexanedione, (2,5-HD) on the neurotoxicity of 0-4-nitrophenylphenylphosphonothioate (EPN) in the chicken. This includes the effect of simultaneous dermal application of EPN and dermal administration or inhalation exposure of n-hexane or related solvents. Also, the effect of MiBK on the neurotoxicity induced by either n-hexane, MnBK, or EPN will be investigated. The effect of n-hexane, and related solvents on the absorption and fate of (14C) EPN will be studied. Finally, we plan to investigate the pharmacokinetics, and metabolism of dermal applications of (14C)-labeled n-hexane, MnBK and 2, 5-HD in the chicken. Inhalation studies will be conducted in the inhalation chambers that were purchased during the first phase of this grant. In neurotoxicity studies the following parameters will be investigated: clinical condition and morphology and distribution of neuropathologic lesions with light and electron microscopes.
PUBLICATIONS


Abou-Donia MB, Makkawy HM, and Graham DG: The relative neurotoxicities of n-hexane; methyl n-butyl ketone; 2,5-hexanediol; and 2,5 hexanediol following oral or intraperitoneal administration in hens. Toxicol Applied Pharmacol 62:369-389, 1982


TITLE

Occupational Neuropathy: Mechanism, Detection, Treatment

PRINCIPAL INVESTIGATOR

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SUMMARY

This is a combined experimental and clinical study of the occupational neuropathy induced by repetitive overexposure to acrylamide monomer. The experimental portion (90% of workload) continues from previous studies which suggest the neuropathic potency of acrylamide is linked to toxic inhibition of certain glycolytic enzymes which are required for the maintenance of axonal transport and nerve-fiber integrity. Proposed studies are designed to test this hypothesis. A tissue-culture model of acrylamide neuropathy will be developed and used to study acrylamide-induced degeneration of living nerve fibers in vitro. Selected drugs (e.g. substrates and inhibitors of glycolysis and Krebs cycle) will be tested for their ability to modify the neurotoxic response to acrylamide in vitro. Agents which protect by delaying or preventing the onset of nerve-fiber degeneration in culture will be tested for their effects on mice repeatedly treated with acrylamide. Initial studies will employ dietary supplementation with sodium pyruvate, an effective therapeutic regimen in rats treated with acrylamide. Treated and control animals will be assayed for neuropathy by quantitative functional, morphological and biochemical assays. The relationship between molecular and cellular mechanisms of acrylamide neurotoxicity will be examined by determining the effects of single and multiple doses on energy-dependent axonal transport. Dose-dependent decrements in fast retrograde axonal transport will be examined in sensory and motor axons and their relationship to changes in fast anterograde transport and distal axonal degeneration determined. The fate of vulnerable glycolytic enzymes transported slowly from neuronal perikaryon to nerve terminal will be examined in the optic nerves of rabbits with advanced acrylamide neuropathy. Finally, studies in rats will examine the current hypothesis that acrylamide induces damage to axons by direct toxic action on nerve fibers. Sites of binding of acrylamide to proteins in peripheral nerves will be determined with the aid of radiolabeled toxin. The clinical portion (10% of workload) will explore the efficacy of the newly developed Optacon Tactile Tester to monitor worker populations at risk for acrylamide and related neuropathies. The major goals of these studies are to develop experimentally proven methods to diagnose, prevent and treat individuals with acrylamide and related occupational neuropathies. These studies respond to some of the research needs specified

PUBLICATIONS


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PROGRAM AREA: Neurotoxic Disorders
GRANT NUMBER: 5 R01 OH00952-05
AWARD PERIOD: 12/01/79 - 11/30/84
FY85 FUNDING: $ 90,307
CUM. FUNDING $478,063

TITLE
Chronobiology and Occupational Health Hazards

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SUMMARY
The long term objective of this study has been to determine what role metabolic rhythms have on influencing response to toxicity from physical stimuli, industrial toxins and therapeutic agents. Among those that have been, or currently are being investigated include: irradiation, paraquat, urethane, malathion, mercuric chloride, insurin, glucagon, epidermal growth factor (EGF), somatostatin, ACTH, and gastrin. The toxicity response in mice to all has been shown to be circadian-stage dependent. Moreover, some of the above polypeptides stimulate RNA and DNA synthesis in a number of tissues including the alimentary canal (EGF, insulin and gastrin) whereas others are predominately inhibitory (glucagon, somastatin, and ACTH), again all responses have been found to be circadian-stage dependent. The aim of the present application is to continue such studies, but also, to determine if the chronobiological findings already gained can be used to reduce overall toxicity.

The model chosen has been cell proliferation in certain regions of the intestinal tract, which also undergoes remarkable circadian variation. Can the fact that fasting, beginning at a certain circadian stage, for a span of 36 hours or less reduce the fraction of proliferating cells and thus be used to protect the gut from damage brought about by: (1) a physical agent such as irradiation which affects the mitotic spindle or (2) a chemical agent such as cytosine arabinoside, which specifically interferes with DNA synthesis? Moreover, will any of the above mentioned peptides, when given before, simultaneously, or subsequent to either a physical or chemical induced injury protect different regions of the gut from damage or enhance repair? Another objective is to gain insight into the mechanism of action of EGF induced cell membrane protein phosphorylation in the gut of normal adult mice and those treated with irradiation.

These studies have relevance for industrial toxicology, gastroenterology, immunology, and endocrinology.

PUBLICATIONS


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Molecular Mechanisms of Diketone Neurotoxicity

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SUMMARY

A variety of industrial and commercially-available chemicals cause a specific toxic neuropathy characterized by abnormal accumulation of neurofilaments within vulnerable axons. The widely used solvents n-hexane and methyl butyl ketone, which have been responsible for many instances of human occupational neurotoxic disease, are converted in vivo to 2,5-hexanedione (2,5-HD), a γ-diketone believed to interact directly with axonal components to induce the observed effects. This proposal is designed to evaluate the hypothesis that γ-diketones react with lysine E-amino groups of neurofilament (NF) and other axonal cytoskeletal proteins in vivo to form hydrophobic 2,5-dialkylpyrrole adducts, that this adduct formation is the critical event for induction of neuropathy, and that the resultant loss of critical lysine moieties and/or changes in protein hydrophobicity causes disruption of the specialized cytoskeletal protein transport mechanism within the axon and subsequent aggregation of NF protein. Since the altered protein persists within the axon and is unable to reach the nerve terminal for proteolysis, nutrient transport into the distal axon is interrupted and axonal degeneration occurs. Although pyrrole adduct formation occurs in non-neural proteins, clearance mechanisms effectively remove altered protein, preventing toxicity. Specific aims designed to prove this hypothesis include quantitation of pyrrole adduct in neural and non-neural tissue protein from rats with prolonged oral exposure to 2,5-HD, and characterization of physico-chemical changes and molecular sites of binding within these proteins. Additional aims are examination of in vivo protein amine binding of non-neurotoxic 2,4-HD, assessment of the ability of this isomer to influence the time course of 2,5-HD neuropathy, and examination of the in vitro protein amine reactivity of the related neurotoxins carbon disulfide, acrylamide, and β,β'-iminodipropionitrile, with the long-range goal of elucidating a common mechanism of action for these compounds. Analytical techniques employed will include polyacrylamide gel electrophoresis, quantitative amino acid analysis, and analytical peptide mapping for identification of altered protein lysine moieties, and HPLC and sedimentation analysis of proteins for assessment of solubility changes and protein aggregation. Lysine reaction products will be characterized by mass spectroscopy, and tissue levels of 2,4- and 2,5-HD will be quantitated by gas.
chromatography. Results will provide substantial progress toward elucidation of the molecular mechanism of action of these important neurotoxic chemicals.

PUBLICATIONS: None to date
Acrylamide Neurotoxicity: Roles of Oxidative Metabolism

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Summary

Acrylamide (ACR) is a neurotoxic agent which produces a central-peripheral distal axonopathy. The axonopathy has occurred in humans following exposure and is induced in animals as a model for investigating pathological processes occurring in ACR-induced axonopathy as well as other primary axonopathies caused by diabetes, alcoholism, vitamin deficiencies, drugs, and other neurotoxins. One proposed mechanism by which ACR produces an axonopathy involves the inhibition of enzymes responsible for ATP formation (energy hypothesis). This proposal addresses this question. More specifically: Does ACR alter oxidative metabolism responsible for energy transformations, decreasing available ATP, producing neuronal compromise and axonopathy? Assays for oxidative enzymes in control and ACR-treated cat spinal cord, peripheral nerve, and liver will determine whether or not ACR inhibits these enzymes. Assays of the same enzymes, in vitro, in the presence of ACR or methylene bis acrylamide (MB ACR) will determine the specificity of enzyme inhibition. Quantitative enzyme histochemical assays in dorsal root ganglion, motor, and Purkinje neurons as well as hepatocytes of control and ACR-treated rats will be used to detect relative changes in enzyme activities of involved, single cell types. The high energy phosphate levels (ATP and CP) in peripheral nerves of chronic ACR-treated cats will be compared to controls to determine the effectiveness of enzyme inhibitions on reduction of available energy. Mitochondria will be tested for their ability to generate ATP after ACR exposure. The association between decreased energy supplies and the neuropathy will be examined with determination of dose-dependent changes in ATP and CP and correlation of these levels with early dose-dependent changes in the rate of fast anterograde axoplasmic transport of radioactively-labelled proteins. The data obtained will contribute significantly to our knowledge of acrylamide-induced axonopathy and will lead to a continuing study of the alterations in oxidative metabolism in other toxic neuropathies.

Publications: None to date
Peripheral Nervous Effects of Workplace Neurotoxins

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As a result of prior research activities, we have identified a need for reproducible, sensitive techniques to evaluate peripheral nervous system (PNS) function in populations exposed to neurotoxic agents. When developed, these PNS tests will be added to an existing system which we have developed to measure the central nervous system (CNS) function in epidemiologic studies of exposed populations. The three tests measure tremor intensity, temperature sensation, and light touch and vibration perception. We propose a project which will consist of examination and modification of the testing apparatus (phase 1), reproducibility testing (phase 2), normative data development (phase 3), testing of three exposed populations (phase 4), and development of a protocol manual guiding use of the system (phase 5). When developed, the PNS tests should expand our ability to study the effects of workplace agents of a chemical or physical nature on PNS function.

PUBLICATIONS: None to date
Title

Symptoms of Neurologic Diseases in Construction Painters

Principal Investigator

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Summary

A cross-sectional, neuroepidemiologic study is being conducted in order to estimate the risk of symptoms of peripheral neuropathy and depression in construction painters when compared with glaziers. Funds are requested for the analysis of data which will have been collected by July 1983, from members of the International Brotherhood of Painters and Allied Trades. The study comprises Mr. Freeman's doctoral dissertation. The study is significant because: (1) prior work suggests painters might risk symptoms of peripheral and central neuropathy, and solvents to which painters are exposed are neurotoxic; (2) we use validated questionnaires, which ascertain effect modifiers, to detect outcomes; and (3) the Union might use the results to focus preventive efforts and more detailed studies on those of its 125,000 painters who appear at risk of neurotoxicity. We selected a stratified (age and geographic locale), systematic sample of 418 painters and 4121 glaziers, members of the same Union. Several sources suggest glaziers have little exposure to neurotoxicants. A mailed, self-administered questionnaire, parts of which we designed and validated in 1981, will ascertain symptoms of neuropathy, occupational exposures, and effect modifiers or confounders (alcohol use, cigarette use, diseases or drugs causing neuropathy, etc). We are compelled to use this approach because of the large size of the population at risk, its dispersion nation-wide in small local unions, and the high cost of neurologic exam by clinicians. The approach has the major advantage of involving International union headquarters, the only organization capable of systematic surveillance and prevention of disease among construction painters who have diverse exposures to solvent paint and who may work for several small contractors in a year. Data analysis will estimate crude and adjusted odds ratios of peripheral neuropathy and depressive symptoms in solvent-exposed painters vs. glaziers; assessment of confounders, and effect modifiers; and tests of dose-response relationships. Both the 4-week period and the one year period preceding the completion of questionnaire will be the focus. Workers, who meet a priori established criteria of symptom frequency, will receive a letter from us advising them to consult their personal physician. Future long-term efforts (industrial hygiene studies, medical examinations, and health education)
require estimates of risk, derived from this study, for establishment of priorities.

PUBLICATIONS: None to date
PROGRAM AREA: Neurotoxic Disorders
GRANT NUMBER: 5 RO3 OH01761-02
AWARD PERIOD: 09/01/83 - 08/31/85
FY84 FUNDING: $ 28,125
CUM. FUNDING: $ 54,585

TITLE

Neurotoxic Esterase and Neurotoxicity

PRINCIPAL INVESTIGATOR

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SUMMARY

Acute or repeated exposure to certain organophosphorus-containing compounds results in a neuropathy in humans which is well modeled in the adult hen. A large body of evidence suggests that alterations in a protein found in nerve, known as “neurotoxic esterase (NTE)”, may be intimately involved in the delayed neurotoxicity of these compounds. Morphological studies indicate that organophosphate neuropathy is best described as a central-peripheral distal axonopathy. However, few attempts have been made to correlate the distribution of NTE with the known location of organophosphate-induced damage. The studies proposed address this important relation. Experiments have been designed to assess the spatial distribution of NTE in a nerve of susceptible species which is known to degenerate following organophosphate exposure (hen sciaticus nerve). Additionally, studies will determine whether NTE in susceptible distal portions of nerve fiber tracts is affected to the same degree by a prototype neurotoxic organophosphate compound (tri-ortho-cresyl phosphate) as that in more proximal less-susceptible portions of nerve fibers. Data will provide, for the first time, information regarding the activity of NTE in organophosphate susceptible and less-susceptible portions of the same nerve fiber. Further studies will determine the role that fast anterograde axonal transport plays in the restoration of NTE activity to the distal portions of vulnerable nerve fibers. Finally, the effect of tri-ortho-cresyl phosphate on anterograde axonal transport of NTE will be evaluated. Data will help clarify the role that NTE plays in the pathogenesis of organophosphate-induced axonopathy. Data obtained from these preliminary studies will be used for the design of future investigations aimed at elucidating the biochemical mechanism of organophosphate-induced distal axonopathy.

PUBLICATIONS: None to date
Neurophysiology of Organophosphorus Neurotoxicity

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The goal of this proposal is to investigate the effect of organophosphorus-induced delayed neurotoxicity (OPIDN) on peripheral nerve and spinal cord electrophysiology. OPIDN is characterized by a silent period 6-14 days before onset of clinical signs and nerve degeneration in both man and sensitive animals. Pathological changes include degeneration in both the peripheral and central nervous system with the distal parts of the longest nerve fibers, both motor and sensory, affected first. In this proposal, the cat will be used as a test animal for recording electrophysiological changes induced by a single dermal dose of tri-o-cresyl phosphate (TOCP), an organophosphorus ester known to induce delayed neurotoxicity. Peripheral nerve function will be assessed using muscle contractile responses to nerve evoked stimuli and stimulus bound repetition which is a nerve terminal related phenomenon. Spinal cord function is to be quantified in terms of both absolute values of monosynaptic reflex responses, and input-output characteristics of the reflex to determine relative amount of transmitter turnover in the spinal cord. Electrophysiological data from animals with OPIDN has been limited. In this investigation, I hope to more clearly elucidate the delayed neurotoxic effects of organophosphorus esters on spinal cord and peripheral nerve physiology in a mammalian species.

PUBLICATIONS

Memory Scanning: A Test of Solvent-Induced Memory Loss

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SUMMARY

Chronic exposure to mixed solvents is known to affect adversely the functioning of the central nervous system. Though a common effect of such exposure is disturbance in short-term memory (STM), the measurement of this function in epidemiologic research has relied primarily on the Digit Span, a relatively crude and inefficient measure. The purpose of this study is to explore the use of an alternative approach to the assessment of STM, the memory scanning technique, as a reliable procedure for application to field research and to employ this test in an evaluation of solvent-exposed workers. Unlike digit span, which measures only success or failure at a memory task, memory scanning provides an estimate of the time in which information stored in STM is retrieved. Psychologic research indicates that memory scanning allows a better understanding of the basic mechanisms of interference with STM than does digit span and that it is able to distinguish the effects of age and alcohol, potential confounders in epidemiologic research.

We have performed a preliminary study, implementing the memory scanning technique (MST) in a population of unexposed workers, which has demonstrated the feasibility of using the MST in field research. This experience has also elucidated the need for specific areas of software refinement. Subsequent to the accomplishment of these changes, a cross-sectional study of painters (N=100), exposed to solvents, and a comparison group of bricklayers and non-solvent-exposed Painters' union members (Total N=100) will be performed. The sensitivity and specificity of the memory scanning technique will be determined relative to both digit span and subjective symptom reports. The interpretation of the memory scan will be facilitated by its use with tests of reaction time and sustained visual attention. A solvent exposure index will be generated for each painter by means of an exposure questionnaire and urinary hippuric acid and methyl hippuric acid concentrations, as indicators of absorption of toluene and xylene, major constituents of solvent mixtures. Development of the memory scanning technique is an important step in the long-term goal of identifying the presence of toxic effects of solvents while they are at an early, potentially reversible stage.

PUBLICATIONS: None to date
PROGRAM AREA: Neurotoxic Disorders
GRANT NUMBER: 1 R03 OH01893-01
AWARD PERIOD: 04/01/84 - 03/31/85
FY84 FUNDING: $18,028
CUM. FUNDING: $18,028

TITLE

Neurobehavioral Effects of Brief Exposure to Lead

PRINCIPAL INVESTIGATOR

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SUMMARY

Studies of workers exposed to lead suggest that neurobehavioral functions such as visual perceptual ability, learning, and memory might be impaired. Thirty-one lead-exposed workers were followed clinically after exposures of less than one year. The applicant plans to compare their performance on neurobehavioral tests which emphasize learning and memory to that of an appropriate control group. To accomplish this, the principal investigator will administer the same battery of tests to working men matched 2:1 to exposed subjects for age and education level. Controls will have blood lead levels less than 20 ug/dl and erythrocyte protoporphyrin levels less than 35 ug/dl. Analysis will consist of comparison of the groups' test scores. This will allow evaluation of the neurobehavioral effects of a relatively brief exposure to lead. Particular attention will be given to effects on learning and memory, functions which have not been extensively looked at in previous studies of lead-exposed workers.

PUBLICATIONS: None to date
PROGRAM AREA: Neurotoxic Disorders
GRANT NUMBER: 5 g03 OH01898-02
AWARD PERIOD: 07/01/83 - 09/30/85
FY84 FUNDING: $ 25,028
CUM. FUNDING: $ 50,003

TITLE
Detection of Polychlorinated Biphenyl Neurotoxicity

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SUMMARY
Polychlorinated biphenyls (PCBs) are widespread contaminants in both the general environment and workplace that have been demonstrated epidemiologically and experimentally to have neurotoxic properties. Enactment of the federal mandate to remove all PCBs from the workplace will further expose workers to PCBs and increases the need for sensitive, objective measures of possible neurological dysfunction.

We propose to undertake a series of experiments using the laboratory rat to assess the feasibility of using peripherally obtained biological specimens such as serum and urine to estimate possible neurological dysfunction caused by acute and subchronic exposure to PCBs. We will assess neurological changes by simultaneously determining catechol and indoleamine (biogenic) neurotransmitters and metabolites in urine, serum, and brain using high performance liquid chromatography with electrochemical detection.

More specifically, we propose to determine: the relationship between systemic exposure to both complex mixtures of PCB congeners and specific isomers and central nervous system (CNS) function as determined by changes in peripheral and central neurotransmitters and metabolites; the relative persistence of these changes following removal from exposure; and the relative neurotoxicities of the major PCB congeners in the adult laboratory rat.

These studies will permit the determination of PCB-induced changes in important CNS neurotransmitters, the relationship between central PCB levels and CNS function and the correlations between urinary and serum estimates of CNS biogenic amine metabolism and the determination of PCB congener body/brain burden ratios. These experiments will permit the validation of peripheral measures of CNS function as an objective screening instrument for the detection of PCB-induced neurotoxicity in the workplace.

PUBLICATIONS
Seegal RF, Bush B, and Brosch KO: Polychlorinated biphenyl induce regional changes in brain norepinephrine concentrations in adult rat. Neurotoxicology, in press
The Effects of Cadmium on the Rat Olfactory System

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Clinical studies of workers exposed chronically to cadmium (Cd) suggest that Cd exposure may result in anosmia. Chronic exposure to Cd in adult rats has been found to cause an increased uptake of Cd in the olfactory bulb. These two lines of evidence suggest that chronic Cd exposure might impair olfaction. Zinc (Zn) has been suggested to play a role in maintaining olfactory function. The mechanisms of toxic action of Cd has been attributed to the interaction of Cd with Zn in many organ systems.

The purpose of the proposed project is to determine what effects chronic low-level exposure to Cd (via inhalation) may have on the rat olfactory system, and by what mechanisms Cd exerts any observed toxic action.

The proposed project will determine whether exposure of rats to chronic low levels of Cd via inhalation impairs olfactory function (i.e., increases the olfactory threshold) in a dose-related fashion. This will be accomplished by using the conditioned suppression technique. Exposure levels were selected so as to permit comparison of the development of deficits in olfactory function with the development of early renal damage. Histological alterations in the olfactory system will be examined by light microscopy. Alterations in odor thresholds and histology will be correlated with Cd and Zn content in the olfactory bulb. The proposed project will also determine whether Cd-induced impairment in olfaction is reversible. Finally, the role of the interaction of Cd with Zn in mediating olfactory effects of Cd will be studied.

The proposed project will not only provide useful and necessary information for the evaluation of the recommended TLV for Cd, but will also help elucidate the mechanisms of toxic action for this agent, as well as serve as a technique which may be useful in assessing the olfactory effects of other toxic compounds.

PUBLICATIONS: None to date
The Effects of Impulse Noise on the Auditory System

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The purpose of this research is to understand the relation between the parameters of impulse noise (peak pressure, duration, number, repetition rate, exposure duration, etc.) and the effects on hearing as assessed by anatomical, physiological, and psychophysical techniques in the chinchilla. Several mechanical or electrical-mechanical devices are used to produce realistic noise impacts. Exposure paradigms are designed to produce asymptotic threshold shifts over exposure durations lasting up to 40 days. Variations of the exposure paradigm include "work week" schedules. Studies are designed to maximize data acquisition to answer basic questions concerning the development of impulse noise damage risk criteria, e.g., validity of the equal energy hypothesis; the effects of noise level during recovery periods, etc. Routine data collection consists of surface preparation derived cochleograms and evoked response and behavioral audiograms and tuning curves. More detailed studies of certain experimental groups will include scanning E.M., as well as more discriminating psychoacoustic measures of hearing. Correlations among the various realms of data are essential for the development of a scientifically based damage risk criteria.


Program Area: Noise-Induced Hearing Loss
Grant Number: 1 R01 OH01518-01A1
Award Period: 08/01/84 - 07/31/87
FY84 Funding: $91,255
Cum. Funding: $91,255

Title
Industrial Noise: Potentiating Interactions

Principal Investigator
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Summary
Synergistic interactions among various ototraumatic agents have been shown to be of importance in determining the hearing loss in a number of industrial situations. The interactions between continuous and impulse noise and vibration and impulse noise will be studied using an experimental animal model (chinchilla). The rationale for these studies is that noise rarely exists as a sole hazard to hearing in many industrial and military work environments. Specific studies will include: (1) Long term combination noise exposures leading to a state of asymptotic threshold shift (ATS). The intensity and spectrum of both the impulse and background noise will be varied to provide a perspective on the noise parameters essential for the "interaction effect". (2) Using an ATS exposure paradigm, the influence of acceleration on the interaction of noise and vibration will be studied; and (3) Psychophysical tuning curves will be used to study changes in frequency selectivity resulting from some of the complex patterns of damage induced by the noise exposures. The final format of the data will include a comprehensive description of the noise exposure, a profile of the animal's hearing capability before and after the treatment and a detailed quantitative morphological analysis of the cochlea. Our problem for this research grant is to experimentally examine the factors that influence the interaction between vibration and various noise exposure paradigms.

Publications

Hamernik RP, Turrentine G, and Wright CG: Surface morphology of the inner sulcus and related epithelial cells of the cochlea following acoustic trauma. Hearing Research, 1984, in press
TITILE

Functional Correlates of Cochlear Injury

PRINCIPAL INVESTIGATOR

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SUMMARY

The major goal of this project is to determine how the magnitude, pattern, and growth of hearing loss and structural damage are altered as the physical characteristics of the stimulus (frequency, intensity, duration, and scheduling of noise) are varied. Another goal is to determine the physiological correlates (as revealed by single-unit studies) of the behavioral changes and anatomical damage induced by exposure to noise. These behavioral, physiological, and anatomical studies share the long-term goal of identifying the relations between functional deficits and injury in the inner ear rather than specifying damage-risk criteria for human exposures.

In addition to these studies, acoustic measures (distortion products; spontaneous otoacoustic emissions) will be made from ear canals of noise-exposed chinchillas. These measures will provide physical indicators of cochlear integrity in the intact animal and information about nonlinear and active processes in the normal and damaged cochlea.

Some of the experimental animals will be trained by food-reward, operant-conditioning techniques so that measures of auditory function (e.g. pure-tone thresholds, frequency DL's etc) can be obtained before, during, and after their exposure to noise. Physiological studies will include thresholds and tuning curves of individual fibers, rate-level functions, and population studies in noise-exposed, behaviorally-trained animals. Histological evaluation of the specimens will include detailed study of plastic-embedded flat preparations so that counts of missing sensory and supporting cells can be made and cytocochleograms prepared for all specimens. Selected regions of the organ of Corti will be sectioned and examined by light and electron microscopy and analyzed morphometrically.

PUBLICATIONS: None to date
PROGRAM AREA: Noise-Induced Hearing Loss
GRANT NUMBER: 1 K01 OH00042-01
AWARD PERIOD: 09/28/84 - 08/31/87
FY84 FUNDING: $ 32,400
CUM. FUNDING: $ 32,400

TITLE

Noise-Induced Hearing Loss and High Blood Pressure

PRINCIPAL INVESTIGATOR

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SUMMARY

For several decades, it has been well documented that chronic noise stress at all levels greater than 90dBA is damaging to the hearing. However, at the present time clear proof of the extra aural noise effects which would be of importance with chronic stressing is not available. A study was recently conducted of occupational noise exposure and the epidemiology of high blood pressure (B/P). The population consisted of 196 male hourly workers from a noise exposed (89dBA) plant and 169 from a less noise exposed plant. Exams consisted of height, weight, pulse, blood pressure, and audiometric testing. Body mass index, alcohol intake, and family history of hypertension were comparable for the two groups. There was no difference in either systolic or diastolic B/P between the exposed and less exposed plant. There was however, a strong relationship between severe noise induced hearing loss (SNHL, defined as 65 dB loss at 3, 4, or 6K Hz), B/P, and hypertension particularly in the older age group after adjusting for several key variables. The results suggest that SNHL and B/P levels are associated and both may be due to long term noise exposure among susceptible individuals. An alternate hypothesis may be that in the older worker, noise exposure in addition to the aging process may lead to poor speech discrimination, discomfort to loud sounds, etc. such that it may result in reduced social interaction and interference in lifestyle. This increased stress on and off the job may affect blood pressure levels. The specific aims of the present study are: 1) further validation of our previous noise and blood pressure study by its replication in a group of men 55-64 who have long histories of occupational noise exposure (N=30) to determine the relationship between SNHL and blood pressure, 2) to carry out further more detailed characterization of the audiometric profile of these men to include air and bone conduction, speech reception threshold, speech discrimination score, presbycusis adj. factor and 3) develop and administer an index of social interaction and lifestyle interference to determine if reduced ability to communicate and hear might be a confounding variable which needs to be controlled for in noise-induced hearing loss and blood pressure studies.

PUBLICATIONS: None to date
Acoustic Stapedius Reflex and Temporary Threshold Shift

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The high degree of variability in temporary threshold shift (TTS) and permanent hearing loss among individuals exposed to the same noise suggests that some people are more "at risk" to noise damage than others. The ability to identify noise susceptible individuals would significantly improve hearing conservation programs and save millions of dollars in compensation and uncalculable dollars in human suffering. There are many factors that relate to susceptibility to noise damage and a test battery approach would appear to be necessary. We are suggesting that the acoustic stapedius reflex (ASR) may prove to be one component of that test battery because of its confirmed role in TTS studies. Short-term noise exposure studies (minutes) indicate that the ASR and TTS in certain acoustic conditions are related. The ASR attenuates low-frequency sound transmission which reduces the total power of the signal reaching the cochlea and consequently reduces the development of TTS in low-frequency, as well as high-frequency regions. Because of the relation between ASR and TTS for short-term exposures, it would seem important to identify if similar relations exist for longer exposure periods (hours). If the TTS that develops following 2-hour noise exposures is related to certain properties of the ASR, e.g. threshold, magnitude, decay, and/or latency, then measurements of its action may prove to be an initial attempt at complying a "noise susceptible" test battery. We propose three studies with this purpose in mind: 1) to identify if correlations exist between ASR and TTS in human subjects exposed for two hours to broad-band noise; 2) to investigate relations between the TTS that develops following 2-hour exposures to octave-band (0.5 and 3.0 kHz) and broad-band noises in two groups of subjects with distinctly different ASR magnitudes; 3) to investigate relations between the TTS that develops following 2-hour exposures to octave-band (0.5 and 3.0 kHz) and broad-band noises in two groups of subjects with distinctly different amounts of reflex decay.

Moul MJ, Gerhardt KJ, and Hepler EL: Further observations on personality pattern and temporary threshold shift. Hearing Instruments, in press
PROGRAM AREA: Noise-Induced Hearing Loss
GRANT NUMBER: 1 R03 OH01829-01A1
AWARD PERIOD: 09/28/84 - 08/31/86
FY84 FUNDING: $20,808
CUM. FUNDING: $20,808

TITLE

Hearing Protection: Selection and Communication Issues

PRINCIPAL INVESTIGATOR

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SUMMARY

Occupationally-related, noise-induced hearing loss is one of the most severe of all threats to the industrial worker. In many industries, noise abatement and hearing conservation programs rely heavily on workers' use of personal hearing protection devices (HPD's) in the presence of high ambient noise. HPD's can indeed be effective in curbing audition problems if selected and used properly. However, available HPD's are known to vary widely in their noise attenuation characteristic and in their acceptability to workers. The proposed two-year research program will address two issues which have direct bearing on the selection of HPD's for specific industrial noise problems.

Industrial noises vary immensely in terms of their sound power spectra, as do the sound attenuation spectra of HPD's. Unfortunately, at present are few data to aid a safety engineer in selecting a HPD for a specific type of noise problem. During the first year of the proposed research, a variety of industrial noise sources will be sampled, spectrally-analyzed, and catalogued. Various types of HPD's (earplugs, ear canal caps, and earmuffs) will then be tested for their attenuation capabilities for each type of industrial noise, using ANSI hearing threshold measurement procedures.

Workers may refuse to wear hearing protection for a variety of reasons, but often because they assume that HPD's hinder verbal communication. At present, there exist little data to support or disprove this assumption. The second year of the project will be devoted to determining the effects of various HPD's on workers speech communication in various intensities and spectra of industrial noise.

Both investigations will be conducted in a semi-reverberant sound chamber in the Auditory Systems Laboratory at Virginia Tech. The project will result in a final document including the results of the industrial noise sampling and guidelines for HPD selection given specific noise problem situations and speech communication issues.

PUBLICATIONS: None to date
PROGRAM AREA: Noise-Induced Hearing Loss
GRANT NUMBER: 1 R43 OH02136-01
AWARD PERIOD: 09/28/84 - 06/30/85
FY84 FUNDING: $ 50,000
CUM. FUNDING: $ 50,000

TITLE

Instrument for Worksite Evaluation of Hearing Protection

PRINCIPAL INVESTIGATOR

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SUMMARY

LONG TERM OBJECTIVE: Prevention of noise-induced hearing loss through development of an instrument for worksite measurement of true effectiveness of insert type hearing protection devices (HPD's) "as worn".  
SPECIFIC AIMS: 1) Determine optimum suprathreshold method for measuring, in high ambient noise, attenuation of HPD's; 2) incorporate this method into prototype instrument for operation at the worksite by unsophisticated testing personnel; 3) establish instrument's technical merit and gather performance data for Phase II development of marketable test instrument.  
METHODOLOGY: 1) Develop computerized laboratory instrumentation for presenting diverse auditory stimuli and recording subject responses. 2) Program instrumentation to provide various suprathreshold tests for evaluating HPD's as worn. 3) Evaluate tests for degree of difficulty, validity, reliability, and test integrity in environmental noise. 4) Build prototype portable field test instrument incorporating most satisfactory test method and instrument configuration. 5) Confirm, in laboratory, validity of the results obtained with the prototype instrument by comparison with results concurrently obtained by standard methods and instrumentation. 6) Conduct initial field testing of the prototype instrument to establish its feasibility and acceptability at the worksite.  
HEALTH IMPLICATIONS: By far, the most common source of communicative disorders below age 60, is noise-induced hearing loss. Incorrectly fitted HPD's are placing a high percentage of noise-exposed workers at risk, thus a need exists for a means of measuring the true attenuation of these devices in the field.  
COMMERCIAL APPLICATION: This instrument could be used in approximately 59,000 U.S. industrial plants.  

PUBLICATIONS: None to date
TITLe

Chloracne: Mechanisms of Pathogenesis

PRINCIpAL INVESTIGATOR

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SuMMARY

We will use hairless mice (Skh/HR and HRs/J) as animal models for studying 2,3,7,8-tetrachlorodibenzo-p-dioxin and 3,4,3',4'-tetrachlorobiphenyl induced "chloracne". Enzymatic changes (aryl hydrocarbon hydroxylase, gamma glutamyl transpeptidase, epidermal transglutaminase, ornithine decarboxylase and S-adenosyl-L-methionine decarboxylase) as well as epidermal cellular retinoic acid binding protein levels, will be monitored during induction of chloracne. The effect of these chemicals on sebaceous and epidermal lipid and androgen metabolism will be studied in in vitro short term biosynthetic experiments using radiolabeled substrates. These same parameters will be studied in human keratinocyte and neonatal mouse keratinocyte tissue culture systems.

PUBLICATIONS


Title

Accommodation and Tolerance in Humans and Guinea Pigs

Principal Investigator

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Summary

Accommodation is a term applied when exposure of skin to irritants and allergens is continued, but the inflammation diminishes, allowing a worker to continue to handle irritants and allergens without difficulty. An original grant focused on the diminished response to irritants. We have learned that continued exposure to irritants may lead to allergic contact dermatitis in 30-40% of those so exposed. Approximately 10% of those regularly exposed to irritants develop a diminished response to the irritant. These accommodated subjects are immunologically normal but have diminished responsiveness to prostaglandin E2 and histamine. Guinea pigs which we have accommodated to maleic acid have diminished responses to chemically similar irritants and somewhat less diminished responses to chemically dissimilar irritants. We have hypothesized that accommodation to irritants represents induction of enzymes and metabolic pathways that allow a more rapid degradation of irritants and/or mediators of the inflammatory response. We will test this hypothesis with histochemical analysis of human skin samples rendered accommodated. The enzymatic pathways which are identified as altered will be studies in our animal model by blocking various components to the pathways in order to identify the critical factors required to handle irritants. We will expand our studies to include accommodation to allergens. This will require monitoring of both Langerhan's cell function and epidermal interleukin activity.

Publications


Rietschel RL: Diagnosis and management of contact dermatitis. Dermatology and Allergy 4:14-16, 1981


Rietschel RL: Irritant contact dermatitis. Dermatology Clinic 2:545-55, 1984

Measurement of Dermal Exposure to Chemical Hazards

PRINCIPAL INVESTIGATOR

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SUMMARY

The purpose of this research is to develop a standard methodology for assessing the location and extent of dermal exposure to pesticides among agricultural workers. The traditional patch technique for measuring direct exposure will be tested by comparing its performance to results obtained through analysis of urinary metabolites of the pesticide. A fluorescent tracer technique will be developed as a new methodology for examining exposure both qualitatively and quantitatively.

It is hoped that this work will result in an accurate and standardized approach to the collection, interpretation and reporting of data related to dermal exposure, both in agriculture and in a variety of industrial settings.

PUBLICATIONS: None to date
Factors in Uptake and Elimination of Chemicals in the Skin

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This project will address the problem of exposure of the skin to chemicals in the workplace through three major steps: 1) a new methodology of photoaffinity labelling in intact skin will be exploited to permit precise monitoring of chemical penetration and localization in the skin and direct identification of risk factors; 2) such studies of chemical penetration and distribution will permit a strategy for developing and monitoring skin cleaning procedures following chemical exposure, and for protecting the skin against exposure.

This series has been made possible by development in this laboratory of a series of photosensitive fluorescent probes which provide a wide spectrum of chemical and physical properties for application in animal models.

3) Finally, the information gained from our new methodology of the qualitative and quantitative details of skin penetration by chemicals even in brief "pre-steady state" exposure will provide the basis for better understanding of the pathogenesis of disorders arising from chemical exposure.

PUBLICATIONS: None to date
Role of Inflammatory Proteinases in Irritant Dermatitis

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SUMMARY

Irritant dermatitis is a major cause of occupational illness. This proposal will investigate the hypothesis that chemical and physical irritants instigate the inflammatory process in skin by activation of pro-inflammatory proteinases and lysosomal hydrolases. We will investigate the effect of model compounds which induce types of irritant dermatitis of human diploid fibroblasts and human epidermal cells in culture. We will study the effect of fibrous glass, pH (especially alkaline pH), metals (chromium, arsenic, and antimony), solvents (benzene, carbon tetrachloride, methanol, acetone) and reactive amines upon the viability, metabolism and activation of proteases and lysosomal hydrolases in our tissue culture cells. We will define whether increases in pro-inflammatory enzymes or lysosomal hydrolases depend upon synthesis of new enzymes, and we will determine the role of microtubules, microfilaments, cyclic nucleotides, and cortisone upon cellular secretion of pro-inflammatory hydrolases and lysosomal enzymes. These studies may disclose pathophysiologic mechanisms in irritancy which can be altered pharmacologically; this would translate into practical therapy which could prevent or ameliorate irritant dermatitis. The effect of these agents upon epidermal cells will also provide fundamental knowledge about metabolism and function of epidermal cells. These studies could have far reaching implications for a variety of occupational irritant chemicals and could provide new means of understanding a large number of occupational illnesses.

PUBLICATIONS


PROGRAM AREA: Dermatologic Conditions
GRANT NUMBER: 1 R01 OH01533-01
AWARD PERIOD: 11/01/83 - 10/31/85
FY84 FUNDING: $ 44,055
CUM. FUNDING: $ 44,055

TITLE
Bioassay for Dioxin: Work Place Related Cutaneous Hazard

PRINCIPAL INVESTIGATOR

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SUMMARY

Occupational and environmental exposure to 2, 3, 7, 8,
tetrachlorodibenzo-p-dioxin (TCDD) and its isomers and congener at low
concentrations induces chloracne and a wide spectrum of clinical pathologies
in humans as well as teratogenesis, carcinogenesis and death in animals.

This proposal is for the development of two in vitro systems, based on
cell culture techniques using relevant biological markers, into routine
assays for the detection and quantification of very low levels of dioxin
congeners and isomers in biological samples. One system is the in vitro
epithelial cell keratinization model of the in vivo hyperkeratinization
response to dioxin exposure resulting in human chloracne. The second system
is based on the development in this laboratory of a subline of epithelial
cells which exhibit a marked increase in density dependent inhibition of
replication and a change from fusiform to "flat-cell" morphology upon
exposure to very low (10-11M) concentration of 2, 3, 7, 8, TCDD. Preliminary
results from this laboratory on testing soot extracts from a dioxin and
dibenzoafuran contaminated building indicate that both these in vitro systems
have the potential for development into rapid and inexpensive quantitative
and qualitative assays for "dioxin-like" acnegenic potential.

The goals of this proposal will be to 1) validate the specificity of
these systems for dioxin congeners and isomers and insure reliability of
these two systems in order to establish them as routine assays, and 2)
initiate preliminary studies to determine the feasibility of using these
assays as a basis for further studies on the detection of dioxin-like
acnegenic activity in serum samples. The latter will form the basis of
future studies to allow routine monitoring of many high risk individuals for
exposure to dioxin congeners and isomers as well as establishing a data base
for use in determining the significance of specific blood levels of these
compounds in regard to subsequent clinical manifestations.

PUBLICATIONS

Gierthy JF, Crane D, and Frenkel GD: Application of an In Vitro
keratinization assay to extracts of soot from a fire in a PCB-containing
transformer. Fundamental and Applied Toxicology, 1984, in press
Gierthy JF and Crane D: Reversible inhibition of In Vitro epithelial cell proliferation by 2,3,7,8-tetrachlorodibenzo-p-dioxin. Toxicology and Applied Pharmacology 74:91-98, 1984

PROGRAM AREA: Dermatologic Conditions
GRANT NUMBER: 5 R01 OH01556-03
AWARD PERIOD: 09/29/82 - 08/31/85
FY84 FUNDING: $55,233
CUM. FUNDING: $149,944

TITLE
Mechanisms of Occupational Leukoderma

PRINCIPAL INVESTIGATOR
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SUMMARY
Occupational depigmentation from phenolic and catecholic skin depigmenters (DP) involves a direct attack on melanocytes. The susceptibility of melanocytes to DP may directly stem from physical and chemical interactions of DP with pigment melanin and/or tyrosinase. Binding of DP to melanin would "select" the pigment as a target for chemical attack. Subsequent redox reactions may involve either electron transfer from DP to melanin or "autoxidation" of DP by O2 (probably catalyzed by tyrosinase). These reactions could undermine the ability of melanin to protect the cell from cytotoxic agents and could result in diffusible reactive species capable of causing melanocyte death. To test this hypothesis we propose to: (1) Measure the binding and redox interactions of selected phenolic and catecholic compounds of widely varying potency with model synthetic melains, melanin-tyrosinase complexes and with melanoproteins extracted from C-57-BL-6 black mice. The kinetics of the above-mentioned redox reactions will be characterized. Experimental conditions will be chosen which maximize a given component reaction while minimizing the others. This will allow an approximate separation of the overall interaction into binding, "autoxidation" and electron transfer components. We will use these results as a basis to dissect the total DP-melanosome interaction into simpler components. (2) Induce hair depigmentation by local subcutaneous or intradermal injection of DP into black mice. The relative potencies of the DP's will be estimated visually and by a turbidimetric analysis of hair melanin in alkaline-sulfide medium. (3) Seek possible correlation between DP potency and the behavior of one or more component interactions. These results will help in filling the gaps necessary for realizing the following long term goals: (a) early detection and prediction of environmental depigmenters, (b) attainment of a reliable regimen for effecting controlled depigmentation, (c) effective use of the appropriate DP's as chemotherapeutic agents in malignant melanoma, and (d) determination of mechanistic similarities and differences between occupational depigmentation and vitiligo.

PUBLICATIONS
Epidermal Langerhans Cells: In Vitro Studies

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SUMMARY

Epidermal Langerhans cells (LC) express many properties characteristic of macrophages and play a pivotal role in the development and elicitation of allergic contact hypersensitivity, and are possibly involved in immune surveillance of cutaneous tumors. The recent development of reproducible immunologic and microscopic techniques for the identification of LC, the ability to isolate and maintain viable LC, immunologic techniques for enrichment in and depletion of LC enable our laboratory to carry out a series of experiments dealing with:

1. Production of biologically active products by LC (lysozyme, prostaglandins, interleukin-1).
2. Identification of factors (alpha-interferon, glucocorticosteroids) affecting the structure (cell surface antigens and receptors) and function (synthesis of biologically active products, alloantigen presentation) of LC.
3. Establishment of a continuous cell line of human LC.

Insights into possible therapeutic regimens to prevent or suppress contact hypersensitivity manifested as allergic contact dermatitis, may be gained with the identification of LC products and modulators. The establishment of a line of human LC would facilitate the study of their biosynthetic properties.

PUBLICATIONS


Berman B and Jaliman D: The Human Interferon System. Dermatologic Allergy and Immunology, in press

Berman B: Langerhans Cells. Dermatologic Allergy and Immunology, in press

Gomez EC and Berman B: The aging skin. Geriatric Clinics of North America Inaugural Issue, in press

Berman B, Duncan MR, Smith B, Ziboh VA, and Palladino MD: Interferon enhancement of HLA-DR antigen expression on epidermal langerhans cells. Journal of Investigative Dermatology, in press


Berman B and Smith B: Aminonide and gamma-interferon modulation of epidermal langerhan cell DR expression. Clinical Research, in press

Berman B and Smith B: Establishment and characterization of a hybridized human epidermal continuous cell line. Clinical Research, in press
A Personal Dosimeter for Exposure to Ultraviolet Light

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We propose to develop a low cost, light weight gas phase actinometer suitable for use as a personal dosimeter for occupational, recreational, or therapeutic exposure to potentially carcinogenic ultraviolet light. For the 200-315 nm region, a tube containing acetaldehyde vapor in air is worn in an exposed place. The methane produced is then analyzed after the end of the shift or after suspected exposure by a gas chromatographic technique. Dilute NO2 is used for the 315-400 nm range, and analyzed by chemiluminescence for the NO2 removal. These detectors make use of our experience in gas phase actinometry developed with NASA support for solar intensity and atmospheric chemistry measurements. The molecules chosen provide a very close match to the required spectral shape for the radiation exposure standards, particularly in terms of the sharp cutoff at long wavelengths. This eliminates any possible interference from abundant long wavelength photons. The proposed dosimeter appears to be very cost effective compared to a more sophisticated electronic dosimeter for UVB recently developed by Davidson, et al., with support from the National Cancer Institute and the Environmental Protection Agency.

In the process of developing this proposal, we determined that solar radiation out-of-doors can violate the recommended exposure in the 315-400 region by as much as a factor of ten.

PUBLICATIONS: None to date
PROGRAM AREA: Dermatologic Conditions
GRANT NUMBER: 1 KO1 OH00017-01
AWARD PERIOD: 09/28/84 - 08/31/87
FY84 FUNDING: $31,270
CUM. FUNDING: $31,270

TITLE
Cutaneous Exposure: Predictive Pathways

PRINCIPAL INVESTIGATOR
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SUMMARY
Skin disease, initiated in the workplace, currently represents a major occupational health problem in the United States. Prediction of the detrimental toxic effects of hazardous chemical exposure is difficult, however, because of the complexity of the percutaneous absorption process and a lack of any consistently identifiable relationship(s) between transport rate and chemical properties. In addition, the very diverse approaches, which have been used to measure skin penetration, further complicate the problem since the extrapolation of results to the human in vivo situation is an exercise requiring often quite unreasonable and, hence, potentially dangerous assumptions. The ultimate goal of the research proposed here is to address this area of occupational health concern. Therefore, our specific aim is acquisition of the ability to predict accurately the toxicokinetics of occupationally-encountered molecules absorbed across human skin in vivo.

The methodological approach will proceed as follows: (1) To establish from the extensive percutaneous absorption literature as broad a database as possible; to review, collate, and file for future access; (a) human and animal in vivo results, (b) in vitro penetration data through excised skin, and (c) proposed pharmacokinetic and diffusional descriptions of skin transport and biodisposition. (2) To develop, on the basis of this information, refined models of the percutaneous absorption process which incorporate both established cutaneous biology and the physicochemical interactions between the penetrant and skin. (3) To assess, in this way, the different experimental approaches to transdermal absorption; to identify, if possible, the predictive capability of the various techniques; and, hence, to specify the most appropriate studies for future determinations of potential cutaneous toxicity.

In the long-term this research is designed to respond to the crucial question: "Can the health hazard from dermal exposure to toxic chemicals be predicted correctly on the basis of fundamental biological and physicochemical principles?" An affirmative response would, it is believed, lead the way to a significant decrease in skin disease of occupational origin.

PUBLICATIONS: None to date
TITLE

Protective Creams to Prevent Poison Oak/Ivy Dermatitis

PRINCIPAL INVESTIGATOR

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SUMMARY

Poison ivy and poison oak dermatitis represent a major occupational, as well as recreational hazard. This is particularly so for forest workers. From 1976 to 1977, Oregon forest workers, insured by the State Accident Insurance Fund, had 27.2% of their injuries and illnesses attributable to dermatitis—most of which was from poison oak and poison ivy. It is our intention to try to develop an active protective cream which will prevent poison oak/ivy dermatitis.

The allergenic principle of poison oak/ivy is known to be 3-pentadecylcatechol (3-PDC) and three related structures with increasing degrees of unsaturation of the 15-carbon side chain. Currently, it is believed that the catecholic portion undergoes oxidation to form the quinone. The quinone, being more reactive than the catechol, then reacts with the thiol and amino groups of proteins to form a 3-PDC: protein conjugate. The resulting conjugate is thought to represent the active allergen.

This sequence of steps could be prevented in one of the following ways: 1) keeping the catechol in the reduced form with reducing agents, 2) providing an alternate substance for the quinone to conjugate with, 3) changing the permeability properties of the skin. Several chemical agents have these properties and, as such, may be able to prevent poison oak/ivy dermatitis.

Evaluation of the efficacy of simple creams containing one or more of these agents may be accomplished simply and reliably using patch tests on human subjects known to be sensitive to poison oak or ivy. The closed patch test technique has been standardized by the North American Contact Dermatitis Group and is a commonly used procedure in dermatology. Testing would involve the application of protective agents to the subject's back followed by challenge with poison oak/ivy extract under occlusion. Different concentrations of protective agents and different vehicles will be tested with the aim of being able to determine the degree of protection provided by the various protective agents.

The validity of the quinone hypothesis of allergenicity will also be evaluated. Conjugates of 3-PDC and an amino acid or protein will be synthesized in vitro, then evaluated using the closed patch test system to determine if the allergenicity of the 3-PDC portion has been destroyed.
PUBLICATIONS

Orchard SM and Storrs FJ: Sensitization to 2-N-Decylaminoethanethiol. Contact Dermatitis 10:248, 1984

Orchard SM: Barrier Creams. Chapter in Dermatology Clinics, October 1984

PROGRAM AREA: Dermatologic Conditions
GRANT NUMBER: 5 R03 OH01830-02
AWARD PERIOD: 07/01/83 - 06/30/85
FY84 FUNDING: $19,590
CUM. FUNDING: $37,851

TITLE

Transdermal Kinetics After Multiple Cutaneous Exposure

PRINCIPAL INVESTIGATOR

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SUMMARY

The percutaneous penetration of chemicals accounts for a significant number of toxic observations. The ability to predict and hence minimize exposure and toxic potential is routinely based upon acute exposure and a single dose transdermal absorption determination. However, the more environmentally and occupationally relevant situation often involves multiple cutaneous exposure for which very little experimental investigation has been performed. The objectives of this project are: (1) to initiate chronic percutaneous absorption studies in an animal model, and (2) to develop and validate a new pharmacokinetic simulation for interpretation and prediction of transdermal penetration kinetics following multiple skin application.

Absorption experiments will be performed in the rhesus monkey. Penetrants to be studied will include chemicals chosen to test the proposed simulation through their diverse absorption characteristics (e.g. benzoic acid, caffeine, testosterone) and toxicologically important substances such as malathion, paraquat, and benzene. Daily application will be made for 2-3 weeks and absorption assessed by monitoring the plasma level or urinary excretion rate of periodic radiolabelled doses (e.g. labelled chemical applied on days 1, 5, 9; cold material on all other days). A new kinetic model, based on distinct physical processes involved in skin penetration, will interpret the data. Rate constants will be found which measure a penetrant's lifetime at various regions within the skin and which control, therefore, the levels of chemical attained both in the barrier and systemically.

In the long-term, this project strives: (a) to determine situations in which acute "single-shot" percutaneous penetration assessments are either useful or deficient for indicating potential toxicity after multiple exposure, and (b) to provide a sound biophysical simulation for transdermal pharmacokinetics that has the ability to predict the time course of skin and systemic disposition following repeated topical applications of penetrant.

PUBLICATIONS


PROGRAM AREA: Psychologic Disorders
GRANT NUMBER: 1 R03 OH02071-01
AWARD PERIOD: 09/28/84 - 08/31/86
FY84 FUNDING: $ 23,683
CUM. FUNDING: $ 23,683

TITLE
A Behavioral Evaluation of Toluene and Ethanol

PRINCIPAL INVESTIGATOR
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SUMMARY
Acute neurobehavioral effects of toluene vapor will be measured by standardization test battery and expressed in "ethanol equivalent units", at the ACGIH recommended action level and TLV. Each subject is exposed for 7 hours to 0, 75, or 150 ppm over 3 consecutive days. A behavioral evaluation of visuomotor skills, visual perception, interference, dexterity and short-term memory will be conducted on a micro-computer given at 8 am, 12 noon, and 4 pm. The behavioral test battery will also determine the effects of ingested ethanol at 0, 0.30, and 0.60 g/kg body weight. The rationale for including the ethanol component is: 1) it serves as a positive control for the toluene experiment, and 2) it permits a comparison of behavioral effects between solvents. Chronic effects of solvent exposure have been equated to premature aging. Similarly, it would be useful to express an acute solvent effect by an index of "ethanol equivalent units" since acute neurobehavioral ethanol toxicity is well described.

The proposed study will be completed in 3 experiments; a pilot study will determine the required number of subjects, and the second and third experiment will examine toluene and ethanol respectively. Subjects are randomly assigned to 1 of 3 orders of exposure presentation (0, 75, 150 ppm). To minimize a possible bias in response to differences in exposure, the odor will be masked by an aromatic agent. Depending on the results of the pilot study an estimated 40 subjects will be in experiment 2 and 3. Paid volunteers with at least 1 year of college, aged 18-35 years old, with no history of solvent exposure, and who consume less than 30 g ethanol per day will be chosen. Inter-subject variation in solvent absorbance will be monitored in expiratory air at each test point, and total toluene uptake will be determined from a 24 hour urinary hippuric acid sample.

The contribution of the proposed study is to examine effects of low concentrations of toluene on human abilities which could result in sub-clinical CNS disorders affecting work, performance, or health. Successful completion of these studies should represent an improvement in research methodology by: 1) using a standardized test battery, 2) by introducing an index of solvent potency in ethanol equivalent units, and 3)
determining if an acute solvent effect exists at relevant industrial exposures which will aid in interpretation of epidemiological investigations of chronic solvent effects. Most of the test battery has been recommended for use in future epidemiological studies by NIOSH and WHO, thus the results will be useful in the design and interpretation of future studies.

PUBLICATIONS: None to date
PROGRAM AREA:  Control Technology Research
GRANT NUMBER:  5 R01 OH01004-04
AWARD PERIOD:  09/01/80 - 07/31/85
FY83 FUNDING:  $45,831
CUM. FUNDING:  $218,027

TITLE

Removal of Contaminating Liquids from Surfaces

PRINCIPAL INVESTIGATOR

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SUMMARY

The primary objective is development of an experimental and theoretical understanding of the mechanics of removal of a contaminating liquid from a solid surface. Criteria are sought through which techniques of removal of contaminating liquids can be better understood and, thereby, improved. Thin liquid films will be deposited on a variety of solid surfaces and then removed by the shearing and impaction of liquid jets. Techniques will be developed for measuring the rate of removal of a film from a surface. Mathematical models will lead to a definition of an efficiency that characterizes the flushing system (jet geometry, speed, viscosity, and surface tension), the contaminating layer (initial thickness, viscosity, surface tension, miscibility in the flushing liquid), and the contaminated surface (surface roughness). Secondary recontamination by splashing and/or contaminant aerosol formation will be studied.

Experiments will be accompanied by theoretical models as an aid to interpretation and correlation of observations.

PUBLICATIONS


150
A Model for Predicting Glove Polymer Permeation

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SUMMARY

The selection of chemical resistant glove polymers for protection from specific solvent exposures in industry has long been a problem. Use of the most effective glove is important; such protective equipment is the last line of defense between the worker and exposure to chemicals that may cause dermatitis or systemic poisoning. Currently, 55,000 chemicals and approximately 10 polymers used in making gloves, offer many possible combinations. One obvious solution to the selection problem would be the systematic development of some predictor of permeation rate or breakthrough time given the polymer and permeant. That is the intent of this proposal.

Previous work by others has indicated, that for some situations, if the solubility parameter (SP) of both polymer and permeant are nearly equivalent, permeation will be high, so that the greater *SP (difference in SP), the lower the permeation rate. In many cases a polymer placed in a series of solvents would be most permeable to the solvent which was most absorbed by the polymer (i.e. most soluble). However, there are exceptions, probably resulting from several factors. The most important may be differences in the components that make up the three dimensional solubility parameter, i.e. hydrogen bonding forces, dipole forces, and dispersion forces. Although *SP may be large, permeation may be significant if one of the above forces for both polymer and permeant is such that it increases the solubility for that polymer/permeant system. Other factors which may effect permeation rates include: crystallinity of polymer, size or shape of permeant molecules; mixtures of permeants, and use of fillers or plasticizers in polymers. It is hoped that a systematic effort to empirically determine the relationship of these factors for several polymers will permit the generation of a predictive model that can be validated.

PUBLICATIONS: None to date
Experimental Pneumoconiosis of Sandblasting Substitutes

PRINCIPAL INVESTIGATOR

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SUMMARY

The use of sandblasting to clean steel structures before applying paint is associated with severe and rapidly progressive silicosis. High morbidity and mortality rates have been noted within a few years of exposure. The U.S. Department of Labor has estimated the number of workers engaged in sandblasting to be 78,000. Recognition of these hazards led to the prohibition of sandblasting in Europe and Australia; in the U.S., sand substitutes are now increasingly being used. They are derived from coal ash residues and slag from smelting furnaces, and comprise various proportions of amorphous silicates of Fe, Al, Ca, Mg, and Ti. The free silica content is only 0.03%.

The objective of this project is to develop a rat model to assess the pulmonary fibrogenic potential of sand substitutes. Fibrotic effect from prolonged exposure to the substitutes will be investigated in both normal and silicotic rats. Silicosis will be induced in one group, followed by exposure to the substitute; the second group will be exposed only to the substitute. After exposure, both groups will be followed for an additional twelve months. Appropriate control rats will be maintained for comparisons. Rats will be sequentially sacrificed for histologic, biochemical assay of collagen, and tissue mineral content evaluations.

This study will assess for the first time the safety of these substitutes. We believe this rat model will have application in delineating and predicting the potential occupational hazards for abrasive blasters with and without pre-existing silicosis. Occupational exposure standards are based on the assumption that the risk of any particular agent is not influenced by exposure to other environmental factors. This study will provide important information on the risk of lung fibrosis from biologic interactions between different inhaled agents, which could affect the future development of occupational standards. More specifically, this project will demonstrate increased risk of progression of silicosis if silicotic sandblaster use these substitutes.

PUBLICATIONS: None to date
TITLE

Optical Study of Lateral Ventilation of Open Vessels

PRINCIPAL INVESTIGATOR

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SUMMARY

This experimental study proposes to employ optical instruments to study and characterize the contamination fields generated by open liquid vessels in an industrial environment. These contamination fields will be visualized and measured quantitatively using a large-field, high-sensitivity schlieren optical apparatus. In particular, the experiments will seek an understanding of lateral ventilation flow patterns and the contamination control effectiveness thereof. The lateral ventilation schemes to be studied will include both suction-type rim exhausters and push-pull type exhausters. In both cases, experimental data will be obtained for the case of an isothermal contaminant/air environment (concentration measurement) as well as for the case of a hot liquid vessel (thermal plume measurement). The experimental data in the form of still and video schlieren images will provide both a qualitative understanding of the flowfield phenomenology and quantitative measures of the concentration and temperature fields. These data may then be used directly in the design of better ventilation schemes, as well as indirectly for the verification of numerical computation methods which have been developed for this purpose. The overall goal of the study is to contribute to the improvement of industrial safety by lowering the risk of contaminant exposure to workers in the vicinity of open vessels containing solvents, degreasers, acid baths, and other harmful agents.

PUBLICATIONS: None to date
Control of Contaminants from Open Vessels

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Open vessels are used in numerous industrial processes in which it is not practical to enclose the vessel. Vapors emanating from the liquid surface are removed by rim exhausters. If air is blown through the slot near the worker and air is withdrawn through the slot on the far side, the system is called a Push Pull System. Push pull rim exhausters are widely used, but little understood devices to prevent vapors from entering the work place. Several variations of rim exhausters are recommended by ACGIH but design criteria are imprecise and in some cases nonexistent.

The objective of this research is to create Computer Aided Design (CAD) procedures for designers to determine whether the contaminant concentrations in the vicinity of the push pull rim exhausters they have designed satisfy OSHA requirements. The specific goals of the proposed research are:

1. Extend existing computer codes to solve the equations of turbulent flow and predict velocity and concentration fields in the vicinity of open vessels equipped with push pull rim exhausters.
2. Conduct experiments to verify numerical predictions.
3. Create computer software and documentation for microcomputers.

None to date
PROGRAM AREA: Control Technology Research
GRANT NUMBER: 1 R43 OH01944-01A1
AWARD PERIOD: 09/28/84 - 05/31/85
FY84 FUNDING: $ 49,875
CUM. FUNDING: $ 49,875

TITLE

Respiratory Hazard Control for Swine Confinement Buildings

PRINCIPAL INVESTIGATOR

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SUMMARY

Our University Consultants have documented through research conducted over the past 7 years, the emergence of an important new respiratory disease hazard to the agricultural population (1-7). Seventy to 90% of the estimated one half to one million workers in swine confinement structures experience respiratory symptoms (1,5), 55% experience chronic bronchitis (6,7), and at least 14 workers have died suddenly from acute respiratory distress and systemic toxicosis (2,4).

The ultimate project goal is to prevent respiratory disease in swine confinement workers by improving the work environment through improved work practices, and the application of cost effective industrial hygiene and engineering controls.

Funds from this SBIR program will allow us to instrument a recently constructed confinement facility and to initiate studies on the relationship between controllable environmental factors and environmental concentrations of ammonia, hydrogen sulfide, methane, carbon dioxide, and aerosols. We will install environmental monitoring devices to establish the level and pattern of environmental pollutant concentrations. We will then evaluate the costs and environmental effects of the type of ventilation system, the ventilation rate, production practices, and the physical and chemical makeup of the feed. These preliminary Phase I studies anticipate a larger series of studies that could result in the development of marketable environmental control technologies or principles that will economically improve the occupational health of a large and growing segment of the farming population.

PUBLICATIONS: None to date
PROGRAM AREA: Control Technology Research
GRANT NUMBER: 1 R43 OH01951-01
AWARD PERIOD: 09/30/83 - 11/30/84
FY84 FUNDING: $43,431
CUM. FUNDING: $43,431

TITLE

Noise Control for Honing Machines – Phase I

PRINCIPAL INVESTIGATOR

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SUMMARY

This proposal is directed toward the Control Technology Research area to be sponsored by the National Institute for Occupational Safety and Health. In Phase I, a systematic investigation will be performed of the noise generated during the process of honing cylinders. This noise is of interest because the exposure of the machine operators to the high frequency tones exceeds the exposure allowed under the OSHA noise regulation. Further, there are no viable retrofit solutions to this problem without severe economic penalties. Preliminary investigations performed by Hoover Keith and Bruce, Inc., have revealed that the noise radiated from the cylinder being honed is not due to the cylinder being excited at its resonance frequencies. The extremely high energy tonal levels (squeals) are either the result of a stick-slip phenomenon between the honing and the cylinder or the result of a resonance of the system of the honing, the head holding the hones, and the hydraulic pressure system which maintains a constant force on the hones. Several methods of vibration generation are discussed. At the conclusion of Phase I, we will understand which of these generation mechanisms is the cause of the squeal. This understanding is critical in developing a generic noise control solution for honing and for other machines which produce similar noise. In Phase II, we will extend this concept to other machinery with tool squeal, for example, turning and hobbing, and develop conceptual noise control treatments for the tool squeal in each of the machines investigated. There is tremendous commercial application for this project which will be realized in Phase III. Several hundred thousand machines expose employees to high levels of tool squeal in violation of the OSHA regulations. A quiet tool system will enable manufacturers to comply with the regulation. In addition, original equipment manufacturers of honing machines and other machines producing squeals will be interested in acquiring such noise control measures for their machines.

PUBLICATIONS: None to date

156
New Methods for Quantitative Respirator Fit Testing

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Quantitative respirator fit testing is required by the Nuclear Regulatory Commission for the health protection of workers in atomic installations, and by the Occupational Safety and Health Administration for workers exposed to lead or acrylonitrile. It is performed by measuring the concentration of a test aerosol leaking into the breathing space between the respirator and the wearer's face. In the conventional technique, di-2 (ethyl-hexyl) phthalate (DOP) has been used as the test aerosol, and the concentrations inside and outside the mask have been determined photometrically through measurements of the scattered light intensities from the DOP clouds. DOP, however, has recently been implicated as a potential human carcinogen.

It is proposed that a continuous-flow condensation nuclei counter (CNC) be adapted for respirator fit testing and a new testing protocol be developed. The CNC enlarges submicrometer-sized, fine particles into the light scattering range, so virtually any non-hazardous cloud of fine particles can be used for fit testing. The use of a special aerosol electrometer will be studied as a potentially even simpler measurement method.

During the second project phase, methods will be developed for fit testing disposable masks which are worn in the presence of silica, coal, or general nuisance dusts. No method exists at present for fit testing masks exposed to such supermicrometer-sized aerosols. It is proposed that an inert, non-toxic dust such as limestone be dispersed by means of a fluidized bed and that the dust concentration for several size ranges inside and outside the mask be determined through use of a modified single particle optical counter.

PUBLICATIONS: None to date
A Fundamental Study of Respirator Air Filtration

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The principal aim of this research is to study the characteristics of particulate air filters of the type used in respiratory protection devices. Commercially available respirator air filters will be studied to determine their efficiency as a function of aerosol particle size in the entire size range of interest in respiratory system protection, namely 0.01 to 10 μm. In addition, the resistance of the filter media and their dust holding capacities will also be measured, and the role of electrical charge in the conventional mechanical and "electrostatic felt" filters will also be determined. A further aim of this research is to make a comparative study of several filter testing methods based on modern aerosol instrumentation and to develop one or more of these to the point where they may be considered for adoption by industry, standards setting groups or regulatory agencies. The end result of this research will be an improved understanding of the characteristics of respirator air filters in general and the availability of improved filter testing methods with potential industrial and practical applications. The research should benefit further respiratory protection device development and encourage the correct use of these devices for worker health protection.

Two approaches will be used to measure the filter efficiency as a function of particle size. In one approach, a monodisperse aerosol will be generated by means of a condensation generator or a vibrating orifice monodisperse aerosol generator, and the aerosol concentration upstream and downstream of the filter will be measured with an electrical aerosol detector or an aerosol photometer. In a second approach, a poly-disperse aerosol will be generated by an atomizer or a fluidized bed dust generator, and the concentration and size distribution of the aerosol will be measured upstream and downstream of the filter with an electrical aerosol analyzer, a condensation nuclei counter-diffusion battery size analyzer, a laser doppler aerodynamic particle size analyzer, and a conventional and laser aerosol size spectrometer. The results will be analyzed and correlated with the modern theory of aerosol filtration based on the Kuwabara-Happel flow field for the cell model.

PUBLICATIONS: None to date
Respirator Performance Model for Particulates

PRINCIPAL INVESTIGATOR

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SUMMARY

The ability of airborne particles to penetrate the filters and facial seal leaks of air-purifying respirators depends strongly on particle size as does the respiratory hazard associated with these particles. Thus, the actual protection factor obtained for airborne particles will depend on the particle sizes present in the workplace environment. The respiratory hazard depends on efficiency of deposition at various sites in the lung and is affected by both the reduction in concentration and the change in size distribution of inhaled aerosol caused by the respirator. With a few exceptions, current respiratory protection factors do not distinguish between exposures to aerosols of different particle size. This study seeks to characterize the effect of particle size distribution on the performance of representative single-use and half-mask respirators. No general data exist to describe the performance of respirators as a function of particle size or particle size distribution.

The first phase (18 months) will measure in the laboratory the performance of respirator filters and facial seal leaks as a function of particle size using a mineral oil test aerosol and a high resolution optical particle counter. Filter measurements will be made at 7 steady flow rates from 2 to 150 L/min. Leakage measurements will be made for three types of leaks and four leakage rates. The second phase (18 months) will use these data to develop a computer model that gives total penetration (filter penetration plus leakage) as a function of particle size for any inhalation flow rate, leak type, and size. The model will be integrated over the breathing cycle associated with five work rates and over log normal size distributions commonly found in industrial situations. The result will give theoretical protection factors for any particle size distribution and for specific jobs where data on work rate, particle size distribution, and leakage rates are available. The model will be applied in conjunction with existing respiratory deposition models to give protection factors based on total and regional deposition as a function of work rate and particle size distribution.

PUBLICATIONS: None to date
In-Mask Monitors and Respirator Breakthrough

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There are many industrial situations in which the use of respirators is the only immediate option for respiratory protection of workers, yet the state of the respirator art has advanced little in recent decades. Among the many areas of respirator design which merit innovative research, this proposal focuses on one set of related topics:

- Quantitative in-mask detection of contaminants
- Better data on both laboratory and field performance acquired through in-mask monitors
- Improved understanding of end-of-service-life and breakthrough leading to better protection and wider use

The technical basis for the proposed work has already been demonstrated for formaldehyde in a NIOSH contract with Molecule Research Corporation. Beyond this good beginning the following remains to be done: optimization of the formaldehyde system, extension of the technology to other respiratory hazards, and application of the results both to worker protection and to improving the data base on which better respirator utilization must ultimately rely. This proposal presents a three year program to achieve these objectives.

PUBLICATIONS: None to date
Comfort and Acceptability of Respiratory Protection Devices

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The specific aim is to identify and quantify the major factors that contribute to discomfort caused by wearing a face mask, with the objective of establishing criteria for the comfort of a mask, and ways to test masks for each of these comfort factors. This analysis should aid in the selection or design of masks that are acceptable to the wearer. Since masks often are not worn during jobs that can cause exposure to potentially injurious inhaled substances, the improvements sought could make them more acceptable and therefore reduce the undesirable exposure. The methods uniquely available in the Pierce Foundation Laboratory are the environmental chamber in which the tests would be done, the special miniature humidity measuring device invented in this Laboratory, moisture measuring techniques including skin wettedness and local sweat rates, skin wettedness and skin temperature relationships with comfort, heat, and moisture flow measurement through porous materials. In addition, methods have been established for measurement of dead space, airway resistance, and CO2 during calibrated exercise tests at measurable rates of body metabolism. We use scales for estimating temperature, skin wettedness and comfort, and devices to measure pressure on the skin surface by means of small flat pressure gauges. The investigators are familiar with air quality criteria and aerosol or dust exposure as well as all of the methods mentioned above, since these have been in use in this laboratory for other projects of a related nature.

PUBLICATIONS: None to date
TITLE

Respirators: Physical and Physiological Considerations

PRINCIPAL INVESTIGATOR

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SUMMARY

It is generally accepted that the modern day requirements for individualized respiratory protective devices far exceeds the available designs of the respirators in current use. This proposed investigation will attempt to:

(i) to provide descriptive psycho-physiological data of the man-respirator interface during maximal work and to relate this data to clinical pulmonary function data so that;

(ii) this descriptive data and its subsequent relationship will be used to provide criterion guidelines for selection of worker capability for wearing a respirator while performing industrial work tasks and finally;

(iii) it is expected that the physiological descriptive data will provide a base to propose design modifications of the currently in-service industrial respirators; to modify current breathing machine certification testing; and to enable development of a computer simulation program for certification testing;

(iv) determine psychophysiological response during maximal and submaximal work performance with and without a respirator and further define;

(a) limiting disease entities;
(b) clinical evaluative procedures and psychological correlates of work performance during respirator wear;

(v) based upon (ii) and (iii) it is anticipated that design modifications can be proposed and man-tested to verify their validity.

Standard work physiology, psychological, clinical, and biomechanical measurement techniques and protocols will be utilized for evaluation of respirator performance during human work. The proposed design modification will also be tested and compared to control evaluations. It is anticipated that the large amount of data expected to be forthcoming will be predictive for respirator design modifications, certification criteria, worker capability to use a respirator and provide a basis for administrators to establish guidelines for worker evaluation.
PUBLICATIONS


TITLE

Optimal Design of Respirator Cartridges

PRINCIPAL INVESTIGATOR

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SUMMARY

The principal aim of the proposed research is to investigate and model the fundamental operational parameters of gas/vapor respirator cartridges so that their design can be optimized. The specific aims include the development of a computer based numerical analysis model of the transport phenomena in the respirator cartridge, verification of the developed model in the laboratory and finally optimization of respirator design in terms of decontamination factor, cartridge life, weight and air flow resistances.

The basic premise to be demonstrated in the laboratory tests is that a few well selected physical measurements, combined with a numerical model for mass transfer in packed beds, lead to the development of respirator cartridges having optimum performance against specific contaminants.

The calculations of mass transfer will be carried out using an implicit finite difference procedure. Such calculations, which would have been impractical or impossible when respirator design was first examined, are now within the reach of the great majority of scientists and engineers working in this area.

This optimization procedure as well as the numerical model for mass transfer can in theory be applied to any combination of adsorbent-contaminant. Here we will apply the procedure to four contaminants, but the methods used here, once this technique has been demonstrated, should be readily transferable to other laboratories.

PUBLICATIONS: None to date
A Model and Tests for Prediction of Respirator Service Life

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The purpose of these investigations is to determine if the Dubinin/Wheeler breakthrough model can be used to predict the service life of respirator cartridges and canisters under use conditions. The model has been shown to be an accurate predictor of absorptive behavior (within +15%) for small carbon beds (less than 10g), using low bed flow rates (less than 0.05 L/S), high inlet concentrations (greater than 10,000PPM) and systems that employ a single contaminant vapor. To extend this model so that it can be used to predict respirator cartridge/canister life it will be necessary to determine if breakthrough times can be accurately predicted for low concentrations of challenge vapor (10-50X Threshold Limit Value), at flow rates consistent with respirator use (light to heavy work rates; 0.3-1.0 L/S), and in environments that contain more than one adsorbable vapor. The additional vapor chosen for these investigations is water. It was chosen because it is a common component of the environment and because it has been shown to effectively inhibit the adsorption of many air contaminants. The time to breakthrough for selected commonly encountered organic vapors will be predicted and experimentally verified. Time to breakthrough will be measured using a carbon challenge apparatus capable of exposing different size carbon beds with known concentrations of two vapors.

The successful extension of the Dubinin/Wheeler Model will enable prediction of appropriate times to change cartridges and canisters based on adsorption theory. Assuming success, experimentation beyond this initial stage will be required to modify the model to accommodate to competing organic vapors and to evaluate the effect of such factors as varying contaminant concentration and cyclic flow. This research could include chamber and field studies to predict service life under actual use conditions. However, the work proposed here is a necessary first step.

PUBLICATIONS: None to date
PROGRAM AREA: Respirator Research
GRANT NUMBER: 5 R01 OH01650-02
AWARD PERIOD: 09/23/83 - 08/31/86
FY84 FUNDING: $108,115
CUM. FUNDING: $167,458

TITLE

Assessment of Respirators Among Agricultural Workers

PRINCIPAL INVESTIGATOR

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SUMMARY

The agricultural sector is both a large (nearly 12 million) and understudied occupational environment. Exposure to complex mixtures of organic dusts and chemicals are responsible for a number of respiratory diseases among agricultural workers— including silo filler's disease, farmer's lung, occupational asthma, and most commonly bronchitis and obstructive airways disease. High rates of respiratory symptoms and airways obstruction have been documented among animal confinement workers and grain handlers. These exposures are often difficult to control, for both technical and economic reasons. Therefore, the use of a respirator in these working environments has become a common request from those adversely affected. Yet, there has been no systematic study of respirator efficacy with exposure to these organic dust and gas aerosols.

Three generic respiratory types will be tested— the single use half mask, the reusable half mask, and the powered air-purifying respirator. Four exposure groups will be tested— 50 swine confinement housing workers, 50 poultry confinement housing or processing workers, 50 grain handlers, and later 12 active farmers with farmer's lung using only the most efficient respirator. Respirator protection factors associated changes in lung function and respiratory symptoms, respirator acceptance, the association between respirator efficacy and acceptance and physical fitness, and the possible effect of smoking will all be evaluated. Ambient and in mask sampling for total dust, endotoxin, and ammonia will provide environmental indicators. Change in respiratory function over an exposure period, change in respiratory and eye symptoms and the worker's response to a questionnaire on various aspects of respiratory acceptance will be the medical indicators.

Results of this study should provide the basis for development of a "model" respiratory program for these and other organic dust exposures.

PUBLICATIONS: None to date
PROGRAM AREA: Respirator Research
GRANT NUMBER: 1 R01 OH02005-01
AWARD PERIOD: 08/01/84 - 07/31/87
FY84 FUNDING: $ 71,100
CUM. FUNDING: $ 71,100

TITLE

Respirator Tolerance

PRINCIPAL INVESTIGATOR

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SUMMARY

This project will evaluate physiologic and psychophysio logic effects of respirator use to develop adequate guidelines for medical certification programs and to facilitate design of better tolerated (and hence more effectively used) respirators. Much previous work has focused upon their effects on maximal work ability and on the ability of an individual to overcome the effects of dead space, resistance, and thermal loads. This project will examine the hypothesis that in most normal and moderately impaired persons, the ability to use a respirator is not determined by these factors, but rather is determined by the adaptation of an appropriate respiratory pattern and by psychophysiological sensitivity to respiratory loads.

Three types of studies will be performed: 1. EXERCISE LABORATORY STUDIES will measure "mechanical" factors (flows, pressure), respiratory timing and pattern, load sensitivity, and metabolic (e.g., oxygen and carbon dioxide volumes) variables in normal and impaired subjects. Measurements will be made at three pseudosteady state exercise levels followed by a ramp period of rapidly increasing exercise in order to identify the factors which critically limit respirator use. Artefact caused by mouthpiece use in previous studies will be estimated. 2. AMBULATORY STUDIES will measure flows, volumes, and respiratory timing and pattern variables under field conditions. 3. DETERMINANTS OF TOLERANCE STUDIES will test load sensitivity, respiratory pattern, and respirator tolerance in a large sample to help define normal variability.

Respiratory timing and pattern measurements will employ a modified respiratory inductance plethysmograph system. It will be done with an FM tape recorder to allow off-line processing and ambulatory use. Load sensitivity will be measured using the "Psychophysical Law", in which perception (P) and Resistance (R) are related: P \( \propto \) R exp(n), "n" representing an individual's sensitivity.

These studies should define the normal response, characterize responses in impaired persons, and determine if tolerance depends primarily on factors other than simple muscle ability to overcome respirator loads.

PUBLICATIONS: None to date
TITLE
Heat Strain: Biophysical and Physiological Evaluation

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New Haven Connecticut 06519

SUMMARY
The present proposal assesses the stress and strain of a warm thermal environment in terms of the various physical and physiological factors involved. The entire physics of heat transfer between the skin surface and the environment can be characterized by a single factor Y, defined as the ratio of the effective sensible heat transfer coefficient (for radiation, convection and conductance) to the insensible heat transfer coefficient (by evaporation). Y is primarily a function of clothing insulation worn, air movement and barometric pressure. The ratio of Y/w, where w is the fraction of the total body skin surface wet with sweat, serves as a biophysical index of the accompanying regulatory strain necessary for thermal equilibrium at any given temperature and ambient vapor pressure. On a psychrometric chart (vapor pressure on ordinate; temperature on abscissa) Y/w is the negative slope of a locus of environmental conditions for which indicators of physiological strain, such as averaged skin and internal body temperature and heart rate, are postulated as equivalent. The temperature at the intersection of this locus with the 50% rh curve serves as a single Effective Temperature (ET*) index of the assessment of various empirical heat stress indices and ET to such physiological responses as cardiac output, blood pressure, heart rate and sweating rate. Heat-acclimated or exercise trained males and females between the ages of 18 to 45 years, clothed and unclothod, will be studied during exposure to high operative temperature (To), humidity (Pa), and during steady and intermittent positive and negative work. Additionally, we shall quantify to what extent local area cooling systems, using evaporatively cooled air, increase heat tolerance limits based on empirical indices.

PUBLICATIONS

Gonzalez RR and Berglund LG: Mass transfer characteristics of the sweating human. 1978 Advances in Biomedical Engineering p173-180, 1978


Gonzalez RR and Sawka MN: Sleep Deprivation Depresses Thermoregulatory Responses to Physical Exercise, Submitted to Science, Dec 1982


TITLE

Human Metabolism of Halothane Mechanisms of Toxicity

PRINCIPAL INVESTIGATOR

James R. Trudell, Ph.D.
Department of Anesthesia
Stanford University Medical Center
Stanford, California 94305

SUMMARY

We will study the toxicity of metabolites of inhalation anesthetics in hepatocytes and a synthetic model of a liver cell formed by reconstituting human cytochrome P-450 and NADPH-cytochrome P-450 reductase into phospholipid vesicles. In our previous studies we have demonstrated that human metabolism of halothane is different from that in rats and monkeys. Therefore, we have developed the methodology to purify human cytochromes P-450 to homogeneity and to reconstitute these cytochromes P-450 along with human cytochrome P-450 NADPH-reductase into a phospholipid vesicle system that is capable of carrying out metabolism like that in liver microsomes. Because of the well defined nature of this system, we are able to study the effect of each specific step of the metabolism of an anesthetic on the surrounding membrane components. Based on the studies of the previous years in which we determined the structure of the free radical metabolites of halothane and carbon tetrachloride and the mechanism of binding of these free radicals to phospholipids, we will proceed to study the molecular mechanism by which these metabolites may initiate destruction of liver cells. We propose three closely related lines of research. First, we will determine the effect of halothane free radical production on lipid peroxidation as well as the function of membrane constituents to which the radicals have bound. Second, we will examine the role of free radical metabolites or phospholipid oxidation products in directing hepatic lysosomes to attack the endoplasmic reticulum. We will observe the initiation of damage in isolated primary hepatocytes by electron microscopy. Third, new information about the existence of sulphydryl-disulfide bonds between membrane anchor-proteins and ribosomes suggests it is essential to control the redox potential of microsome or hepatocyte suspensions, and motivates a new study of alteration of ribosome binding and function by free radical metabolites. We will attempt to correlate toxicity in animals and humans with specific metabolic pathways occurring in the liver. Our goal will be to define those conditions that should be avoided in order to prevent significant toxic metabolism in patients and operating room personnel.
PUBLICATIONS

Trudell JR: Molecular basis for unitary theories of inhalation anaesthesia. Inhalation Anesthesia Today and Tomorrow p45-52, 1982

Trudell JR and Bosterling B: Interactions of Cytochrome P-450 with phospholipids and proteins in the endoplasmic reticulum. Membrane Fluidity in Biology Vol I:201-233, 1983


Trudell JR and Bosterling B: Evidence for leukotriene A4 as an intermediate in the conversion of 5-HPETE to leukotriene B4 catalyzed by cytochrome P-450. Biochemical and Biophysical Research Communications 115:995-1001, 1983


Trudell JR and Bosterling B: Production of 5- and 15-hydroperoxyeicosatetraenoic acid from arachidonic acid by halothane free radicals generated by UV-irradiation. Anesthesiology 60:209-213, 1984

Trudell JR, Bendix M, and Bosterling B: Hypoxia potentiates killing of hepatocyte monolayers by leukotrienes, hydroperoxyeicosatetraenoic acids, or calcium ionophore A23187. Biochimica et Biophysica Acta 803:338-341, 1984
TITLE

Potentiation of Haloalkane Renal Injury by Ketones

PRINCIPAL INVESTIGATOR

Esther M. Brown, Ph.D.
Department of Veterinary Anatomy
University of Missouri
Columbia, Missouri 65211

SUMMARY

Chlorinated hydrocarbons are used extensively in industrial settings. While these chemicals can produce liver and kidney injury in employees exposed to toxic concentrations, safe working conditions have been established for these solvents when they are employed singly. However, other common industrial solvents have been shown to enhance the hepato and nephrotoxic properties of certain haloalkane solvents. Thus, normally safe concentrations of a haloalkane may become hazardous due to the presence of an additional chemical agent in the working environment.

Animal models have been developed which have a certain predictive value for determining the ability of solvent mixtures to interact and produce a potentiated hepatotoxic response. However, similar models, capable of predicting the potentiation of haloalkane-induced nephrotoxicity, do not exist. Recently, the applicant has demonstrated that three ketonic solvents can interact with chloroform, a representative haloalkane, to produce a potentiated nephrotoxic response in rats. Based on this observation, the project is designed to: (1) determine if ketonic solvents, as a class, are capable of potentiating haloalkane-induced nephrotoxicity; and, (2) determine the mechanism(s) by which the nephrotoxicity of chloroform was potentiated by ketonic solvents. These objectives will be fulfilled by performing a pharmacodynamic analysis of the potentiation phenomenon produced by five representative ketones and by analyzing the effects of ketones on the renal chloroform biotransformation capacity. In addition, the ability of ketonic solvents to alter the nephrotoxic properties of other haloalkanes will be determined. Ultimately, it is hoped that an animal model capable of predicting the ability of chemicals to interact and produce a potentiated nephrotoxic response will be developed.

PUBLICATIONS


Hewitt WR and Brown EM: Nephrotoxic interactions between ketonic solvents and halogenated aliphatic chemicals. Fundamentals of Applied Toxicology 4, 1984, in press

Title

Breath Sampling for Industrial Solvent Exposure

Principal Investigator

Michael S. Morgan, Sc.D.
University of Washington
Mail Stop SC-34
Seattle, Washington 98195

Summary

The objective of this project is the development and laboratory testing of a convenient technique for sampling trace compounds in exhaled air. Breath analysis has several theoretical advantages over other methods of monitoring worker exposure to industrial solvents, but its utilization has been hindered by unreliable or impractical sampling technology. The method proposed here is based on an air purifying respirator, to which is added a sampling cartridge in the exhaled air port. Thus, a worker under examination would inhale contaminant-free air, but his exhaled air would pass successively through layers of activated charcoal cloth and a bed of desiccant. Any solvent vapor in exhaled air, reflecting absorption into the bloodstream, will be collected on the charcoal cloth, which will then be removed and analyzed. The weight gain of the desiccant will provide a measure of the volume of exhaled air sampled. The system will be thoroughly tested with several organic solvents using a controlled-atmosphere chamber. The concentrations used will extend into the parts per billion range, representing a major improvement in sensitivity over previous methods.

Publications: None to date
Lead and Cadmium Toxicity Related to Industrial Exposure

Jules B. Puschett, M.D.
School of Medicine
University of Pittsburgh
1191 Scaife Hall
Pittsburgh, Pennsylvania 15261

SUMMARY

Industrial exposure to cadmium and lead is a widespread and serious occupational problem. This proposal is directed toward evaluating the effects of these two metals in single and combined exposure, on several levels: 1) in the human subject, 2) in experimental animals and 3) in vitro test systems. It is proposed that those workers at risk because of occupational contact with these two heavy metals be examined to determine if there are abnormalities of renal function and of skeletal function that will serve as hallmarks of early toxic effects, prior to the development of established (and potentially irreversible) disease. Furthermore, utilizing the clearance and micropuncture techniques as well as quantitative histomorphometry in the experimental animal, both the acute and chronic effects of lead and cadmium on the kidney and bone can be evaluated. The causes and mechanisms of the toxic effects of these substances will be studied at the cellular level with the in vitro techniques of isolated tubular perfusion and brush border vesicle studies. If successful, these experiments should provide better early warning detection systems for toxic effects of lead and cadmium and should add to our basic knowledge as to how their toxic effects are mediated. An understanding of the pathogenetic sequence should not only aid in the prevention of disease by exposure avoidance, but may allow us to manipulate the internal as well as external environment so that these substances may be rendered less harmful if inhaled or ingested. Furthermore, better treatment modalities for subjects intoxicated with lead or cadmium should result from the prosecution of the studies outlined in this proposal.

PUBLICATIONS: None to date
PROGRAM AREA: Other Occupational Concerns
GRANT NUMBER: 1 R01 OH01531-01
AWARD PERIOD: 12/01/83 - 11/30/85
FY84 FUNDING: $ 55,534
CUM. FUNDING: $ 55,534

TITLE
Effect of Unusual Workshift on Dichloromethane Toxicity

PRINCIPAL INVESTIGATOR
Gary P. Carlson, Ph.D.
Department of Pharmacology and Toxicology
School of Pharmacy and Pharmacal Sciences
Purdue University
West Lafayette, Indiana 47907

SUMMARY

Over the past several years a number of industries have adopted unusual or novel workshifts increasing the number of hours worked per day to 12. The basic objective of this proposal is to examine the possibility that workers on such schedules may be at increased risk to the toxic effects of industrially encountered chemicals due to the increased time of exposure and decreased time for recovery. The compound of interest is dichloromethane. A major aim is to determine if exposure to this compound for a novel workshift results in an increased body burden of the compound and enhanced toxicity. Rats will be exposed for one day, one week or two weeks to either a normal workweek schedule or an unusual 12 hour, 4 day week schedule. Assessment will be made of dichloromethane concentrations in blood and fat both immediately following exposure and prior to reexposure. Toxicity will be measured as increases in carboxyhemoglobin, serum sorbitol dehydrogenase and hematocrit. A second aim is to examine the influence of exposure concentration on these differences due to workshift by studying four concentrations ranging from 50 to 1000 ppm. An additional aim is to study the effects of confounding factors including additional carbon monoxide exposure, exercise, and overtime. Such studies should provide empirical data for adjusting current standards for exposure to protect the health of the worker in novel workshifts.

PUBLICATIONS: None to date
PROGRAM AREA: Other Occupational Concerns
GRANT NUMBER: 5 R01 OH01542-02
AWARD PERIOD: 09/30/83 - 08/31/86
FY84 FUNDING: $62,456
CUM. FUNDING: $136,609

TITLE

Benzene Toxicity in Bone Marrow Precursor Cells

PRINCIPAL INVESTIGATOR

Daniel Wierda, Ph.D.
Department of Pharmacology and Toxicology
West Virginia University Medical Center
Morgantown, West Virginia 26506

SUMMARY

Occupational exposure to benzene represents a significant hazard to certain individuals in the workplace. Chronic exposure to benzene can cause multiple clinical disorders that are related to the general hematotoxicity of benzene. However, benzene itself is not considered the ultimate toxicant but is transformed into metabolites that react with cellular macromolecules and interfere with normal development of bone marrow precursor cells. Experiments in this proposal are designed to investigate the cellular mechanism of toxicity of benzene and benzene metabolites on bone marrow immuno/hemopoiesis. The polyhydroxy metabolites of benzene to be studied include benzoquinone, benzoin, catechol, hydroquinone, and phenol. A primary objective of these studies is to examine the relationship between the in vivo and in vitro effects of benzene metabolites on marrow precursor cell proliferation and differentiation. In this study, it will be determined how benzene and its metabolites can alter precursor T- and B- lymphocyte development as well as precursor granulocyte/monocyte development. Emphasis will be applied to discerning changes between maturational development versus cellular proliferation. An important part of the study will be to investigate the role of stromal cells of the marrow hemopoietic microenvironment in metabolite-induced marrow toxicity. Stromal cells constitute cells that are capable of promoting specific hemopoietic proliferation and development. A detailed examination of alterations in the normal process of precursor cell differentiation and maturation will result in greater understanding of the molecular events triggering myelotoxicity in individuals exposed to benzene or benzene metabolites.

PUBLICATIONS: None to date
TITLE

Chromium Distribution and Toxicity in Mammalian Cells

PRINCIPAL INVESTIGATOR

Edwin M. Uyeki, Ph.D.
University of Kansas
39th Street at Rainbow Boulevard
Kansas City, Kansas 66103

SUMMARY

We will study the intracellular distribution of chromium and the mechanisms of chromium toxicity in mammalian cells. With Cr(VI), increased SCE frequency occurred at 0.01 micromolar, whereas the inhibition of cell proliferation occurred at 1.0 micromolar. Cr(III) was much less effective. Our working hypothesis is that the genotoxic effects of Cr(VI) are causally related to the antiproliferative effects.

We will study the transport of 51-Cr (VI and III) into cells and of their distribution in intracellular organelles. We expect that chromium toxicity is associated with changes in chromatin conformation (DNA superstructure).

Our plan is to: study cytogenetic changes by chromium by using assays which measure chromatid aberrations, chromosomal aberrations and SCE: utilize computer-aided cell sizing equipment to detect small changes in cell growth and cell size; develop chromium-resistant and chromium-transformed cells; use a variety of analyses to monitor alterations in these cell variants; study the effects of chromium on the uptake of nucleotide precursors and cellular nucleotide pools; use the following preparations for biochemical studies: intact cells, permeabilized cells, nucleoids and isolated chromosomes; study the effects of chromium on the fidelity of DNA synthesis, and on the conformation of chromatin in these preparations. We are assembling computer-aided instrumentation for karyotyping and identifying SCE's on individual chromosomes.

PUBLICATIONS

TITLE

Evaluation of Occupation Listed on Routine Data Sources

PRINCIPAL INVESTIGATOR

Annette Stemhagen, Dr.P.H.
New Jersey State Department of Health
John Fitch Plaza
CN 360
Trenton, New Jersey 08625

SUMMARY

Surveillance of occupational information on routine data sources such as death certificates and cancer registry abstracts is often used to identify disease problems and to develop hypotheses for further epidemiologic study.

The proposed research is intended to compare, for a sample of incident New Jersey cancer cases and controls, occupational data which has already been collected from three independent sources: personal interview, cancer registry abstracts, and death certificates. The information recorded on the death certificate and cancer registry abstract will be compared with the more accurate information collected from a lifetime occupational history obtained during personal interview.

The long term objective of this research is to suggest to epidemiologists and other researchers the most effective uses of routinely collected occupational data by describing how accurately these data sources characterize the usual occupation and industry of individuals. If the death certificate or cancer registry abstract often describe last occupation/industry or current occupation/industry, then the value of these sources for occupational epidemiologic studies will need to be reassessed.

PUBLICATIONS: None to date
TITLE

Improved Personal Protection at Hazardous Waste Sites

PRINCIPAL INVESTIGATOR

Steven P. Levine, Ph.D.
University of Michigan
1420 Washington Heights
Ann Arbor, Michigan 48109-2029

SUMMARY

The materials handled at a hazardous waste site are normally analyzed only for compatibility (acid, base, organic, etc.) because a complete analysis is too costly and time consuming for the many thousands of samples that must be characterized at a hazardous waste site. The resultant data are sufficient to prevent explosions or the generation of toxic gas clouds from the mixing of incompatible materials (such as conc. acids and bases). However, very little information is generated that is useful from a toxicological standpoint. For example, a waste that is classified as “organic” may contain acrylic paint, ink, phenol-formaldehyde resin, benzaldehyde, or parathion. Thus, it is difficult to use a knowledge of material content to guide worker protection programs. A need exists for a rapid chemical analysis screening procedure that will give chemical data beyond that which is obtainable via compatibility tests.

This proposal addresses the concept of using Fourier Transform Infra-red Spectrometry (FTIR) to fulfill the above need. The rapid scanning capability of a FTIR is used to allow the high sample throughput required of any assay technique employed at a hazardous waste remedial action project. An attenuated total reflectance (ATR) cell is utilized to overcome the problem of samples that would normally be considered opaque to infra-red energy because of suspended solids. The identity of compounds and compound classes will be determined through the use of computerized library search and spectral interpretation techniques. These data will be compared to those from both compatibility testing and gas chromatographic-mass spectrometric methods. A compatibility testing scheme incorporating the FTIR-ATR protocol into personal protection strategies will then be formulated.

Several extended compatibility testing schemes have been proposed that may fulfill some of the above objectives. These rely on wet chemistry and are time consuming (1.3 man hr/sample), require skilled chemists to carry out, and are prone to interferences. FTIR would provide a rapid, cost-effective complement to existing methods, thereby providing data for many classes of compounds. This would allow personal protection strategies to be formulated on the basis of sound industrial hygiene principles.

PUBLICATIONS: None to date
TITLE

Symptom Reports and Mortality in Paper Workers

PRINCIPAL INVESTIGATOR

Everett E. Logue, Ph.D.
Department of Epidemiology
School of Public Health
The University of North Carolina at Chapel Hill
Rosenau Hall 201H
Chapel Hill, North Carolina 27514

SUMMARY

The proposed study will examine the relationship between self-perceived health status and all-cause and cause-specific mortality in a cohort (N=1,224) of paper manufacturing workers (ages 35-69 at intake) followed for 22 years. It is hypothesized that there will be a positive association between the number of symptoms reported at intake and subsequent mortality. Symptom reports will be measured by the Cornell Medical Index (CMI). The date and cause of death will be ascertained by securing death certificates from Vital Statistics Offices in North Carolina and the surrounding states in the Southeast. The company personnel office will be used to ascertain vital status and the last known address. After the information on the death certificates is nosologized and keyed, it will be linked with existing automated files in the Department of Epidemiology at the University of North Carolina. These files contain CMI responses, coded occupational titles, and risk factor information collected at intake. The data analysis will be based upon conventional (stratum-specific and standardized) mortality rates, and upon parametric and nonparametric survival techniques with covariates. Supplementary analyses could compare the mortality experience of the paper manufacturing cohort with the mortality experience of the general population (national, state, and multiple-county level data).

PUBLICATIONS: None to date
TITLE

Anemometry Related to Workplace Contaminant Distribution

PRINCIPAL INVESTIGATOR

Robert C. Spear, Ph.D.
School of Public Health
University of California
322 Warren Hall
Berkeley, California 94720

SUMMARY

The research will examine the relationship between air circulation in a room and the spatial and temporal distribution of a contaminant gas. It is proposed to quantify and map air circulation patterns using a recently developed anemometer which can accurately resolve the 3-dimensional wind vector in a typical room. An empirical model describing the relationship between air circulation and the contaminant distribution will be derived from real time wind vector and air concentration data collected under controlled conditions. It is proposed to evaluate the performance of this empirical model, in predicting changes, in the contaminant distribution, when air circulation and source location are changed.

Air circulation patterns in a workroom are fundamentally related to the dispersal of contaminants and thus influence worker exposures. Yet the quantitative influence of air circulation on the contaminant distributions is poorly understood. This research addresses this issue since it is aimed at the development of a method for directly measuring air circulation and quantitatively relating this measurement to the distribution of a contaminant.

PUBLICATIONS: None to date
Acute Biochemical Toxicology of Aliphatic Nitriles

Paul Vincent Kaplita, Ph.D.
Department of Pharmacology and Toxicology
Dartmouth Medical School
Hinman Box 7650
Hanover, New Hampshire 03756

Aliphatic nitriles are commercially important, but toxic, organic chemicals. Each day, thousands of American workers are potentially at risk from nitrile poisoning. The acute toxicity of these nitriles has been attributed to the slow metabolic release of cyanide. In the case of succinonitrile, the reaction appears to be mediated via a two-step pathway firstly through hepatic oxidases and then by alcohol dehydrogenase. I propose to test other nitriles by: Specific Aim 1; establishing the effectiveness of alcohol dehydrogenase inhibitors to antagonize the acute toxicity of nitriles in mice, Specific Aim 2; testing multiple doses of alcohol dehydrogenase inhibitors with or without coadministration of thiosulfate as antidotal regimens in mice, Specific Aim 3; determining the ability of oxidized nitriles to serve as substrates for alcohol dehydrogenase in vitro, and Specific Aim 4; testing the ability of unusual microsomal enzyme inducers to potentiate the acute toxicity of nitriles in mice. My objective is to develop a better understanding of nitrile bioactivation and detoxification, and to suggest safer and effective antidotes for the management of human intoxication.

None to date
PROGRAM AREA: Other Occupational Concerns
GRANT NUMBER: 1 RO3 OH01993-01
AWARD PERIOD: 08/01/84 - 07/31/85
FY84 FUNDING: $ 6,528
CUM. FUNDING: $ 6,528

TITLE

Development of a New Sampling/Analysis Method for Ozone

PRINCIPAL INVESTIGATOR

Kenneth Dale Blehm, Ph.D.
Colorado State University
110 Veterinary Science Building
Fort Collins, Colorado 80523

SUMMARY

The objective of this work is to develop a new solid sorbent sampling and analytical method for ozone. The current methods for ozone lack specificity, reliability, and convenience (all are liquid absorption methods). Several reactions with ozone will be investigated to determine which ones give the most reproducible reaction products which can then be analyzed. All reactions will be based on ozonolysis, the reaction of ozone with unsaturated compounds. Once the reactions have been studied and the most reliable chosen, the starting material will be coated on an inert substrate and tested against known concentrations of ozone. Once a working method has been developed (i.e., sample media and analytical procedure), the method will be “validated” according to NIOSH guidelines, tested for common interferences (SO2 and NOx), and then field tested against a standard method or direct reading instrument.

PUBLICATIONS: None to date
PROGRAM AREA: Other Occupational Concerns
GRANT NUMBER: 1 R03 OH02045-01
AWARD PERIOD: 09/28/84 - 08/31/86
FY84 FUNDING: $ 15,000
CUM. FUNDING: $ 15,000

TITLE

Formaldehyde Molecular States in the Gas Phase

PRINCIPAL INVESTIGATOR

David Francis Utterback, Ph.D.
Maple and Shaw
California State University
Fresno, California 93740

SUMMARY

The objective of this research is to further investigate the molecular species of formaldehyde present in the gas phase. Research by this investigator has found that the total formaldehyde content of vapors at equilibrium with a formalin solution consisted of methylene glycol, methylvlar and the first three oligomers of polyoxymethylene glycol monomethyl ethers. This research also developed a novel gas phase trimethylsilylation procedure utilizing BSTFA with analysis of the TMS ethers by GC/FID. Further validation of the gas phase derivatization procedure is proposed through reaction of a series of low molecular weight alcohols and glycols with BSTFA in the gas phase and the products analyzed by GC/FID. Yields will indicate the feasibility of gas phase trimethylsilylation as a quantitative method of analysis for polyoxymethylene glycols and the glycol monomethyl ethers. A formaldehyde vapor generating system will then be constructed and the molecular species of formaldehyde produced will be analyzed by a matrix of procedures that, in combination, may distinguish between monomeric formaldehyde, s-trioxane and the polyoxymethylene glycols. Operating parameters of the generating system will be adjusted to obtain maximum monomeric formaldehyde production. Next, gas phase monomeric formaldehyde at known concentrations will be reacted with water vapor at several temperatures between 20 and 40 degrees C in a dynamic dilution/reaction system and the products analyzed by the matrix of analytical procedures for formaldehyde and methylene glycol in order to calculate the gas phase equilibrium constant for the reaction. Results of this research will allow determination of the formaldehyde molecular species present in atmospheres: (1) where human exposures occur, (2) utilized for animal exposures in toxicological assessment and, (3) in the humid airways of respiratory systems where carcinogenic effects have been observed.

PUBLICATIONS: None to date
Title
Compliance with OSHA Health Standards: Methods and Cases

Principal Investigator
Carol A. Jones, Ph.D.
School of Natural Resources
University of Michigan
Dana Building, Room 2041
Ann Arbor, Michigan 48109

Summary
The first goal of the proposed study is to address methodological issues in the cross-plant analysis of OSHA inspection data on ambient air levels of hazardous substances. The second goal is to analyze the OSHA inspection data for two major health hazards regulated by OSHA, in order to assess the impact of OSHA policies on worker exposure levels. The data for the analysis will be extracted from the principal investigator's computer tapes containing the complete records from the OSHA Management Information System (MIS) of all OSHA inspections from 1972 through 1983. Analysis of the data presents substantial statistical problems, namely: (1) achieving comparability across plants in the specification of violations; (2) measurement error associated with industrial hygiene measurements; and (3) bias in the selection of plants and locations within plants to take hygiene samples.

One anticipated product will be a paper providing a formal treatment of the range of statistical issues associated with analysis of the hygiene data pooled across plants. The paper will provide a useful framework for subsequent use of the data (in conjunction with data from other sources) for studies of the impact of regulatory standards and enforcement policies on ambient air levels of hazards and for studies of the health effects associated with ambient air levels.

A second anticipated product will be a longitudinal study of one or two hazardous substance(s) regulated by OSHA, in addition to a re-analysis of the asbestos data presented in the principal investigator's dissertation. As with the earlier asbestos study, the focus will be on analyzing the determinants of agency decisions regarding enforcement policy (where to inspect, how much to fine when violations are detected) and company behavior regarding the control of exposure levels. The Heckman technique for correcting sample selection bias will be employed. The model will be estimated using maximum likelihood methods. With the Heckman correction technique, it is possible to project exposure performance for the universe of firms (with potential exposures) on the basis of the performance of inspected firms. Substances under consideration include silica, lead, coke oven emissions, noise, vinyl chloride, and carbon monoxide. Others may be considered.

Publications: None to date
Safety and Sensitivity: Ethical Issues in Identifying and Protecting High-Risk Persons in the Workplace

PRINCIPAL INVESTIGATOR

Roger E. Kaspersion, Ph.D.
Department of Government
and Geography
Clark University
950 Main Street
Worcester, Massachusetts 01610

SUMMARY

The central question addressed by this project is: How should society respond to the differential sensitivity of workers to technological hazards in the workplace? To help answer this question, the project will undertake the following tasks: a review of scientific progress in conceptualizing and identifying differential sensitivity, considering the implications of these developments for policies and practices in the workplace; an inventory and analysis of ethical issues posed by differential susceptibility to hazards on-the-job; a detailed analysis of the alternative responses made in three cases—lower back injury, smoking linked with asbestos exposure, and lead exposure; development of methodologies, based in theories of social justice, for assessing equity in occupational exposures to risk; and development of ethical guidelines and strategies that can incorporate project results in occupational health and safety policies and practices. Project results will be made available in major scholarly and popular journals, and at professional and public meetings and hearings, as well as in an integrated scholarly monograph.

PUBLICATIONS: None to date
AWARD SUMMARY OF ALL ACTIVE GRANTS DURING FY84

<table>
<thead>
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<th>Grants from FY84 Budget ($6.50M)</th>
<th>Competing Grants</th>
<th>Total Grants</th>
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<td>Research Project Grants (R01)</td>
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<td>Career Development Grants (K01)</td>
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Grants from FY83 Budget ($4.74M)
| Research Project Grants (R01) | 0 | $0       | 16 | $1,079,201 |
| Small Grants (R03)            | 15 | $253,814 | 15 | $253,814 |
| Other Grants                  | 0 | $0       | 2  | $143,541  |
| **Subtotal**                  | 15 | $253,814 | 33 | $1,476,566 |

Grants from FY82 Budget ($4.74M)
| Research Project Grants (R01) | 0 | $0       | 2  | $155,007  |
| Other Grants                  | 0 | $0       | 0  | $0       |
| **Subtotal**                  | 0 | $0       | 2  | $155,007  |

Grants from all Years
| Research Project Grants (R01) | 26 | $2,051,256 | 76 | $6,456,519 |
| Career Development Grants (K01) | 12 | $386,148   | 12 | $386,148   |
| Small Grants (R03)            | 30 | $518,858   | 46 | $849,345   |
| Other Grants                  | 4  | $149,875   | 7  | $336,847   |
| **TOTAL**                     | 72 | $3,106,137 | 141 | $8,028,859 |

* Does not include three inactivated grants due change of status of principal investigators.
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<th>Program Area</th>
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* Exceeds FY84 Budget of $6,501,000 because total includes all grants that were active at any time during FY84.
### DISTRIBUTION OF GRANTS BY REGION AND STATE

141 GRANTS TOTALING $8,028,859, Amounts in $1000's

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<td>Georgia</td>
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<td>Michigan</td>
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# INDEX OF GRANT NUMBERS BY GRANT ACTIVITY

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<thead>
<tr>
<th>Grant Number</th>
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<th>Current Funding</th>
<th>Year</th>
<th>Page</th>
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## Career Development Grants (K01)

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