NIOSH GRANTS

RESEARCH and DEMONSTRATION PROJECTS

ANNUAL REPORT
Fiscal Year 1990

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

CDC
CENTERS FOR DISEASE CONTROL

NIOSH

RESEARCH AND DEMONSTRATION GRANTS

FISCAL YEAR 1990

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

April 1991

DISCLAIMER

Mention of company names or products does not constitute endorsement by the National Institute for Occupational Safety and Health.

DHHS (NIOSH) Publication No. 91-106

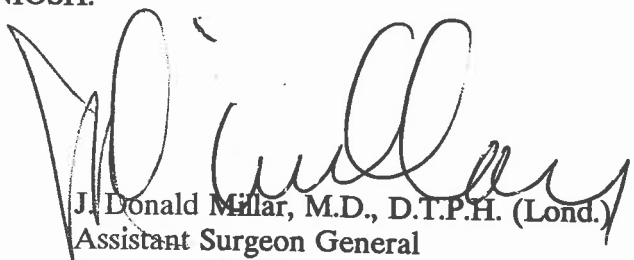
FOREWORD

The National Institute for Occupational Safety and Health (NIOSH) is mandated under the provisions of the Occupational Safety and Health Act of 1970 and the Federal Mine Safety and Health Amendments Act of 1977 to develop recommendations for protecting workers of the United States against diseases and injuries related to risks on the job. In carrying out this mission, NIOSH plans, directs, and coordinates a national program of research, training, and related activities. In addition to a substantial program of intramural research, NIOSH supports outstanding extramural research as a major component of its scientific activity.

Since 1984, NIOSH investment in both intramural and extramural research has focussed on "The Ten Leading Work-Related Diseases and Injuries." These are listed as the first ten entries in Section H. ("Funding Priorities") in the program announcement included in this report (pages 4-10). In addition to the leading occupational diseases and injuries, our program priorities include research on control techniques and respiratory protection because of the crucial importance of these areas to prevention.

To provide guidance on priorities for action, NIOSH sponsored the development of "Proposed National Strategies for the Prevention of Leading Work-Related Diseases and Injuries." Implementation of the Prevention Strategies requires commitment from a broad array of organizations and scientific and professional disciplines. Our extramural research program is an important means of facilitating progress in these preventive efforts.

Because the strengths of the extramural research program are the creativity and special resources that are available in the scientific community, we publish this report to stimulate submission of proposals for research of high quality on significant problems of occupational safety and health. We invite the interest of investigators in the biomedical sciences, engineering, and related disciplines. By including descriptions of all active grants during fiscal year 1990 (October 1, 1989 to September 30, 1990), we intend to provide a readily available source of information on the status and scope of the research grants program of NIOSH.



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

TABLE OF CONTENTS

INTRODUCTION

The organization of this annual report on the NIOSH research grants program is designed to facilitate the reader's understanding of the types of extramural research projects supported under the primary areas of NIOSH's interest with respect to the leading work-related diseases and injuries.

- Summaries of the supported projects are grouped according to these major areas of interest, as indicated in the *Table of Contents*.

- Within each program area, projects are grouped by type of grant (e.g., research project grant, career development grant, and small grant).

  Note: *See the program announcement beginning on page 4 for descriptions of these grant types and other types that NIOSH awards.*

Each grant summary contains administrative information about the grant, followed by a synopsis of the project and any publications that have resulted to date.

- Principal investigators prepare the summaries for inclusion in this report. The synopsis is an explanation of the nature of the project and a discussion of results, with sections on *Importance to Occupational Safety and Health, Objectives, Methodology, and Significant Findings*.

- Publications are listed so that the reader may gain more information about the projects than is given in the brief summaries. Although some citations are not yet published or may not be retrieved easily, they have been included for the sake of providing maximum information.

  Note: *Should there be an interest in more information, principal investigators should be contacted directly.*

Statistics on the number and amount of funds awarded by grant type, program area, and region/state are given in tabular form at the end of the report. Indices are included for ease in locating particular grants if the reader knows the grant number, the principal investigator, or the grantee institution.

Note: *See glossary on page 3 for an explanation of the components of a grant number.*

Suggestions on content or format of this report to make it more useful to the reader would be welcomed. The process of assembling the report begins in the fall of each year, so comments should be received at least by the end of September.

- Inquiries or ideas should be addressed to:

  NIOSH Grants Office
  1600 Clifton Road
  Building 1, Room 3053, MS - D30
  Atlanta, Georgia 30333
  404/639-3343

ACCESS TO LITERATURE

In addition to the publications listed after each grant summary, readers may wish to refer to NIOSH's Document Information Directory System (DIDS).

What is DIDS?

DIDS is a computerized data base of documents that are produced from NIOSH-sponsored research (intramural and extramural). This data file is maintained by the NIOSH Division of Standards Development and Technology Transfer to track the following types of NIOSH documents: Alerts, Current Intelligence Bulletins, criteria documents, control technology reports, hazard evaluation and technical assistance reports, industrywide study reports, contract reports, health and safety guides, Fatal Accident Circumstances and Epidemiology (FACE) reports, research grant publications and reports, training documents, testimony, and books, book chapters, and journal articles authored by NIOSH employees.

What Specific Data does DIDS include?

Each entry includes the document title, publication number, subject index terms, availability information, NIOSHTIC accession number, name of principal investigator for research grants, and complete citations for books, book chapters, and journal articles. Nearly 9,100 entries are currently maintained in the system.

Who may use DIDS and What is the Cost?

DIDS is used primarily by NIOSH personnel, but searches are often requested by persons from industries, unions, academic institutions, and the general public. Searches are free of charge.

How can a Search be Requested?

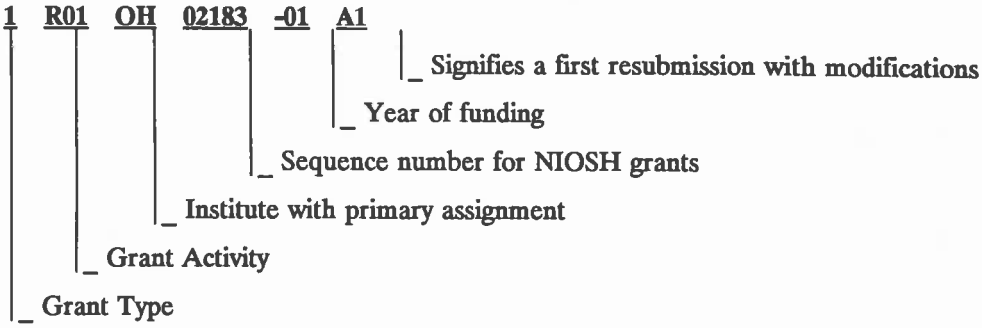
Contact NIOSH at the following address and telephone number:

Technical Information Branch
Division of Standards Development and Technology Transfer
National Institute for Occupational Safety and Health
4676 Columbia Parkway
Cincinnati, Ohio 45226-1998
Telephone: 513/533-8350

GLOSSARY

Grant Number - The identification number assigned to a grant application

EXAMPLE: 1 R01 OH02183-01A1



Typical Codes:

Grant Type

- 1 - New Competing application
- 2 - Competing renewal application
- 5 - Noncompeting continuation application
- 7 - Change of grantee institution

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

The 10 leading Work-Related Diseases and Injuries

- Occupational Lung Diseases
- Musculoskeletal Injuries
- Occupational Cancers
- Traumatic Injuries
- Cardiovascular Diseases
- Disorders of Reproduction
- Neurotoxic Disorders
- Noise-Induced Hearing Loss
- Dermatologic Conditions
- Psychological Disorders

Related Research Categories of High Priority

- Control Techniques
- Respirator Research
- Other Occupational Needs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control
National Institute for Occupational Safety and Health

ANNOUNCEMENT NUMBER 923

RESEARCH AND DEMONSTRATION GRANTS
RELATING TO OCCUPATIONAL SAFETY AND HEALTH

A. INTRODUCTION

The Centers for Disease Control (CDC), National Institute for Occupational Safety and Health (NIOSH), is soliciting grant applications for research and demonstration projects relating to occupational safety and health.

B. AUTHORITY

This program is authorized under the Public Health Service Act, as amended, Section 301 (42 U.S.C. 241); the Occupational Safety and Health Act of 1970, Section 20 (a)(29 U.S.C. 669[a]); and the Federal Mine Safety and Health Amendments Act of 1977, as amended, Section 501(30 U.S.C. 951). The applicable program regulations are in 42 CFR Part 52.

C. 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.

D. AVAILABILITY OF FUNDS

The support mechanisms for this program are the individual research project grants (R01); demonstration project grants (R18); special emphasis research career award (SERCA) grants (K01); and small grants (R03). In FY 1990, $6,897,315 was available to fund 70 grants: 30 new grants were funded for $3,320,500 and 40 non-competing continuations were funded for $3,576,815.

E. BACKGROUND

The NIOSH is mandated to develop recommendations for protecting workers of the United States against diseases and injuries related to risks on the job. In 1983, NIOSH published a suggested list of ten leading work-related diseases and injuries as part of a national goal to improve the health of the American people through prevention activities. These are listed as the first ten entries in Section "H. FUNDING PRIORITIES." To provide guidance on priorities for action, NIOSH sponsored the development of "Proposed National Strategies for the Prevention of Leading Work-Related Diseases and Injuries." Working groups composed of NIOSH scientists drafted proposed national strategies for these ten areas of concern. These strategies were refined in a process involving two national meetings of health and safety professionals representing academia, management, organized labor, professional associations, and voluntary organizations. Implementation of the Prevention Strategies requires commitment from a broad array of organizations and scientific and professional disciplines. The extramural research program is an important means of facilitating progress in these preventive efforts.

Additional guidance is found in the document, "Healthy People 2000: National Health Promotion and Disease Prevention Objectives." The document contains measurable objectives and strategies for creating a healthier society over the next decade. The objectives and strategies are organized broadly into 3 major categories:

Health Promotion, Health Protection, and Preventive Services. There are a total of 22 priority areas. The tenth priority area, "Occupational Safety and Health," is applicable to this program announcement. Overall objectives in this priority area are to reduce work-related deaths, injuries, and illnesses. Research is needed on the following: identification of new stressors affecting workers, new measurement tools for assessing worker exposures, biomarkers of workers' exposure and response, identification of populations and individuals at special risk of work-related disease and injury, mechanisms of insult and intoxication, hazard surveillance, disease and injury identification and surveillance, development of control approaches, and effective use of controls.

F. PURPOSE

The purposes of this grant program are to develop knowledge on the underlying characteristics of occupational safety and health problems in industry and on effective solutions in dealing with them; to eliminate or control factors in the work environment which are harmful to the health and/or safety of workers; and to demonstrate technical feasibility or application of a new or improved occupational safety and health procedure, method, technique, or system.

G. MECHANISMS OF SUPPORT

The types of grants NIOSH supports are described below. Applications responding to this announcement will be reviewed by staff for their responsiveness to the following program requirements. Grants are usually funded for 12-month budget periods in project periods up to 5 years for research project grants and demonstration project grants; up to 3 years for SERCA grants; and up to 2 years for small grants. Continuation awards within the project period are made on the basis of satisfactory progress and on the availability of funds.

1. Research Project Grants (R01)

   A research project grant application should be 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.

2. Demonstration Project Grants (R18)

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

3. Special Emphasis Research Career Award (SERCA) Grants (K01)

   The SERCA grant is intended to provide opportunities for individuals to acquire experience and skills essential to the study of work-related hazards, and in so doing create a pool of highly qualified investigators who can make future contributions to research in the area of occupational safety and health. SERCA grants are not intended either for individuals without research experience or for productive, independent investigators with a significant number of publications and of senior academic rank. 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.

   Candidates must: (1) hold a doctoral degree; (2) have research experience at or above the doctoral level; (3) not be above the rank of associate professor; (4) be employed at a domestic institution; and (5) be citizens or non-citizen nationals of the U.S. or its possessions or territories or must have been lawfully admitted to the U.S. for permanent residence at the time of application.

This non-renewable award provides support for a three-year period for individuals engaged in full-time research and related activities. Awards will not exceed $50,000 in direct costs per year, and the indirect cost rate applied is limited to 8 percent of the direct costs, excluding tuition and related fees and equipment expenses, or to the actual indirect cost rate, whichever results in the lesser amount.

A minimum of 60 percent time must be committed to research, 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. Related activities may include research career development activities as well as involvement in patient care to the extent that it will strengthen research skills. Fundamental/basic research will not be supported unless the project will make an original contribution for applied technical knowledge in the identification, evaluation, and/or control of occupational safety and health hazards (e.g., development of a diagnostic technique for early detection of an occupational disease). Research project proposals must be of the applicants' own design and of such scope that independent investigative capability will be evident within three years. At the completion of this three-year award, it is intended that awardees should be better able to compete for individual research project grants awarded by NIOSH.

SERCA grant applications should be identified as such on the application form. Section 2 of the application (the Research Plan) should include a statement regarding the applicant's career plans and how the proposed research will contribute to a career in occupational safety and health research. This section should also include a letter of recommendation from the proposed advisor(s) and a letter from the supporting institution agreeing to the minimum 60 percent time commitment to research for three years.

4. Small Grants (R03)

The small grants program 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. Eligible applicants are predoctoral graduate students, post-doctoral researchers (within 3 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 include appropriate justification for this arrangement. Biographical sketches are required for the person actually doing the work as well as the supervisor and other key consultants.

Small grants may be awarded for project periods of up to two years and are thereafter continuable by competitive renewal as a research project grant. Salaries can be requested for necessary support staff such as laboratory technicians, interviewers, etc. Salary of the principal investigator, as well as that of the junior investigator (if university policy requires that a more senior person to be listed as the principal investigator), will not be allowed. Awards will not exceed $15,000 in direct costs per year, and the indirect costs based upon the negotiated indirect cost rate of the applicant organization. Small grant applications should be identified as such on the application form.

H. FUNDING PRIORITIES

The NIOSH program priorities, listed below, are applicable to all of the above types of grants listed under "G. MECHANISMS OF SUPPORT." These priority areas represent the leading diseases and injuries related to risks on the job, and NIOSH intends to support projects that facilitate progress in preventing such adverse effects among workers. 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, but the rationale for the significance of the research to the field of occupational safety and health must be developed. Potential applicants with questions concerning the acceptability of their proposed

work are strongly encouraged to contact the individuals listed in this announcement under "O. WHERE TO OBTAIN ADDITIONAL INFORMATION." The NIOSH Program Priorities are:

1. Occupational 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 infraction
6. Disorders of reproduction: infertility, spontaneous abortion, teratogenesis
7. Neurotoxic disorders: peripheral neuropathy, toxic encephalitis, neuroses, extreme personality changes (exposure-related)
8. Noise-induced loss of hearing
9. Dermatologic conditions: dermatoses, burns (scalding), chemical burns, contusions (abrasions)
10. Psychological disorders: personality disorders, psychoses, debilitating stress
11. Control Techniques: new technology performance evaluation, preconstruction review, equipment redesign, containment of hazards at the source, fundamental dust generation mechanisms, machine guarding/avoidance methods, explosion control, removal of emissions after generation, dispersion models, monitoring and warning techniques, technology transfer
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

I. INCLUSION OF MINORITIES AND WOMEN IN STUDY POPULATIONS

Applicants should include, where feasible and appropriate, women as well as men and minorities in the study of populations for all clinical and research efforts and to analyze, where appropriate, differences among these populations. If women and minorities are not to be included, a clear rationale for their exclusions should be provided.

J. APPLICATIONS SUBMISSION DEADLINES AND REVIEW DATES

Applications should be submitted on Form PHS-398 (revised 10/88). State and local government applicants may use Form PHS-5161-1 (revised 3/89); however, Form PHS-398 is preferred. Forms should be available from the contacts listed under "O. WHERE TO OBTAIN ADDITIONAL INFORMATION," or from:

Office of Grants Inquiries
Division of Research Grants
National Institutes of Health
Westwood Building - Room 449
5333 Westbard Avenue
Bethesda, Maryland 20892

The original and six copies of the PHS-398 or the original and two copies of the PHS 5161-1 application must be submitted to the address below on or before the specified receipt dates also provided below. A mailing label is provided in the Form PHS-398 application package.

Division of Research Grants
National Institutes of Health
Westwood Building - Room 240
5333 Westbard Avenue
Bethesda, Maryland 20892

The timetable for receiving applications and awarding grants is given below. This is a continuous announcement, consequently, these receipt dates will be on-going until further notice.

Research and Demonstration Project Grants:

Receipt Date*	Initial Review	Secondary Review	Earliest Possible Start Date
February 1	June/July	September	December 1
June 1	Oct/Nov	January	April 1
October 1	Feb/Mar	May	July 1

*Competing continuation deadlines are 1 month later.

SERCA and Small Grants

Receipt Date	Initial Review	Secondary Review	Earliest Possible Start Date
March 1	June/July	August	November 1
July 1	Oct/Nov	December	March 1
November 1	Feb/Mar	April	June 1

Applications must be received by the above receipt dates. To guard against problems caused by carrier delays, retain a legible proof-of-mailing receipt from the carrier, dated no later than one week prior to the receipt date. If the receipt date falls on a weekend, it will be extended to Monday; if the date falls on a holiday, it will be extended to the following work day. The receipt date will be waived only in extenuating circumstances. To request such a waiver, include an explanatory letter with the signed, completed application. No request for a waiver will be considered prior to receipt of the application.

Applicants should follow the guidance provided in the application package. Please refer to Announcement Number 923 when requesting information. It is essential that applicants type "NIOSH Announcement Number 923" in item 2 on the face page of the PHS-398 application form or at the top of the face page of the PHS 5161-1.

K. EVALUATION CRITERIA

Applications received under this announcement will be assigned to an Initial Review Group (IRG). The IRGs, consisting primarily of non-Federal scientific and technical experts, will review the applications for scientific and technical merit. Notification of the review recommendations will be sent to the applicants after the initial review. Applications will also be reviewed for programmatic importance by NIOSH. Awards will be made based on results of the initial and secondary reviews, as well as availability of funds.

1. The initial (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.

   - Documentation of cooperation 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, the applicant's research career plan in occupational safety and health, and the degree to which the applicant's institution offers a superior research environment (supportive nature, 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.

2. In the secondary review, the following factors will be considered:

   - The results of the initial review.

   - The significance of the proposed study to the research programs of NIOSH.
     1) Clearly linked to occupational safety and health.
     2) Contributes to achievement of the research objectives specified in Section 20 (a) of the Occupational Safety and Health Act of 1970 and in Section 501 of the Federal Mine Safety and Health Amendments Act of 1977.
     3) Makes original contribution for applied technical knowledge in the identification, evaluation, and/or control of occupational safety and health hazards.
     4) Addresses a question(s) that when answered will provide knowledge upon which to take prevention action or to address another question(s) in a logical sequence of investigations toward preventing a health or safety problem. The logical sequence need not be defined rigorously, but there must be a likelihood of producing useful results. Judgment of the importance of the question(s) to be addressed is based on: a) the magnitude of the problem, b) the severity of the effects, c) the extent of the application of the results, or d) the advance in knowledge to be derived by the project.

- National needs and balance of awards across funding priorities
- Policy and budgetary considerations.

Questions regarding the above criteria should be addressed to the Technical Information Contact listed under "O. WHERE TO OBTAIN ADDITIONAL INFORMATION."

L. TECHNICAL REPORTING REQUIREMENTS

Progress reports are required annually as part of the continuation application (75 days prior to the start of the next budget period). The annual progress reports must contain information on accomplishments during the previous budget period and plans for each remaining year of the project. Financial status reports (FSR) are required no later than 90 days after the end of the budget period. The final performance and financial status reports are required 90 days after the end of the project period. The final performance report should include, at a minimum, a statement of original objectives, a summary of research methodology, a summary of positive and negative findings, and a list of publications resulting from the project. Research papers, project reports, or theses are acceptable items to include in the final report. The final report should stand alone rather than citing the original application. Three copies of reprints of publications prepared under the grant should accompany the report.

M. EXECUTIVE ORDER 12372 REVIEW

Applications are not subject to review as governed by Executive Order 12372, Intergovernmental Review of Federal Programs.

N. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER (CFDA)

The Catalog of Federal Domestic Assistance number is 93.262.

O. WHERE TO OBTAIN ADDITIONAL INFORMATION

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.
Building 1, Room 3053, Mail Stop D-30
Atlanta, Georgia 30333
Telephone: (404) 639-3343

For Business Information Contact:

Ms. Carole J. Tully
Grants Management Specialist
Grants Management Branch, PGO
Centers for Disease Control
255 E. Paces Ferry Road, N.E.
Room 300, Mail Stop E-14
Atlanta, Georgia 30305
Telephone: (404) 842-6630

1. The initial (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.

   - Documentation of cooperation 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, the applicant's research career plan in occupational safety and health, and the degree to which the applicant's institution offers a superior research environment (supportive nature, 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.

2. In the secondary review, the following factors will be considered:

   - The results of the initial review.

   - The significance of the proposed study to the research programs of NIOSH.
     1) Clearly linked to occupational safety and health.
     2) Contributes to achievement of the research objectives specified in Section 20 (a) of the Occupational Safety and Health Act of 1970 and in Section 501 of the Federal Mine Safety and Health Amendments Act of 1977.
     3) Makes original contribution for applied technical knowledge in the identification, evaluation, and/or control of occupational safety and health hazards.
     4) Addresses a question(s) that when answered will provide knowledge upon which to take prevention action or to address another question(s) in a logical sequence of investigations toward preventing a health or safety problem. The logical sequence need not be defined rigorously, but there must be a likelihood of producing useful results. Judgment of the importance of the question(s) to be addressed is based on: a) the magnitude of the problem, b) the severity of the effects, c) the extent of the application of the results, or d) the advance in knowledge to be derived by the project.

- National needs and balance of awards across funding priorities
- Policy and budgetary considerations.

Questions regarding the above criteria should be addressed to the Technical Information Contact listed under "O. WHERE TO OBTAIN ADDITIONAL INFORMATION."

L. TECHNICAL REPORTING REQUIREMENTS

Progress reports are required annually as part of the continuation application (75 days prior to the start of the next budget period). The annual progress reports must contain information on accomplishments during the previous budget period and plans for each remaining year of the project. Financial status reports (FSR) are required no later than 90 days after the end of the budget period. The final performance and financial status reports are required 90 days after the end of the project period. The final performance report should include, at a minimum, a statement of original objectives, a summary of research methodology, a summary of positive and negative findings, and a list of publications resulting from the project. Research papers, project reports, or theses are acceptable items to include in the final report. The final report should stand alone rather than citing the original application. Three copies of reprints of publications prepared under the grant should accompany the report.

M. EXECUTIVE ORDER 12372 REVIEW

Applications are not subject to review as governed by Executive Order 12372, Intergovernmental Review of Federal Programs.

N. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER (CFDA)

The Catalog of Federal Domestic Assistance number is 93.262.

O. WHERE TO OBTAIN ADDITIONAL INFORMATION

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.
Building 1, Room 3053, Mail Stop D-30
Atlanta, Georgia 30333
Telephone: (404) 639-3343

For Business Information Contact:

Ms. Carole J. Tully
Grants Management Specialist
Grants Management Branch, PGO
Centers for Disease Control
255 E. Paces Ferry Road, N.E.
Room 300, Mail Stop E-14
Atlanta, Georgia 30305
Telephone: (404) 842-6630

Epithelial Surface Proteins: Markers of Cancer Risk

William W. Merrill, M.D.
Yale University School of Medicine
P.O. Box 3333, 109-LCI
New Haven, Connecticut 06510

Program Area: *Occupational Lung Diseases*
Grant Number: *5 R01 OH02114-03*
Start & End Dates: *01/01/86 - 12/31/89*
Funding Level: *$116,868 ($410,648 Cum)*

Importance to Occupational Safety and Health

Workers who are exposed to the fibrous silicate asbestos experience an increase in several diseases of the lower respiratory tract. The two most frequent and dramatic are a predisposition to bronchogenic carcinoma and a chronic inflammatory and fibrotic reaction in lung parenchyma termed "asbestosis". Both diseases are found with increased frequency in those with an occupational asbestos exposure. Cigarette smoking increases the risk of cancer and may also increase the risk of asbestosis in these workers. We assess metaplasia as an index of cancer risk with two probes (histologic and biochemical), and study fibrosis with standard lung function tests, and study mechanisms of injury as revealed by cells and proteins recovered from bronchoalveolar lavage. Our goal is to find early markers or predictors of these diseases. Such markers might allow therapy at an early stage prior to development of irreversible pathology.

Objectives

There were two independent objectives in these studies. Metaplasia was assessed in this population by performing bronchial biopsies and quantifying the degree of metaplasia in the biopsies by a qualitative 4-point scale. In addition to the biopsy technique, we quantified the amounts of two proteins synthesized locally in the bronchial mucosa to determine if the biochemical assessment of metaplasia was possible in these workers.

Fibrogenesis was assessed functionally by pulmonary function testing. Subsequently, inflammatory characteristics of the lower respiratory tract were related to this functional assessment.

Methodology

We have recruited 55 subjects for evaluation. These included three normal volunteers and 52 workers with a past history of occupational exposure to asbestos and a past or current history of tobacco usage. All subjects received a chest radiograph and pulmonary function testing. A subgroup of the asbestos workers also received quantitative gallium scanning of the lung. Following these studies, the subjects had flexible fiberoptic bronchoscopies performed after topical anesthesia. After a careful evaluation of the airways, multiple small biopsies were obtained from branch points in the right lung. Subsequently, the bronchoscope was wedged in the lingula and a bronchoalveolar lavage was performed. One aliquot of the lavage fluid was frozen and subsequently sent to collaborators in Belgium for asbestos body counts. The remainder of the lavage fluid was processed for quantitation of total cells recovered and cellular differential. A variety of proteins were quantified by micro ELISA assays. Subsequently, we related the amount of free secretory component (a glycoprotein synthesized by normal bronchial mucosal cells) and the keratins (proteins released by metaplastic bronchial epithelial cells) present in BAL fluid to the degree of metaplasia noted in the bronchial biopsies.

Additionally, we attempted to relate functional impairment suggestive of fibrogenesis (diffusion capacity) with the numbers and types of inflammatory cells present in bronchoalveolar lavage fluid and with the quantitative estimate of gallium uptake obtained previously.

Significant Findings

Characterization of the population: The asbestos worker study population was comprised of subjects with positive chest x-rays. Approximately 50% of the population had pleural plaques, while the remainder had parenchymal opacities. All had at one time been cigarette smokers; however, 60% had stopped smoking from 1 to 32 years prior to bronchoalveolar lavage. Each subject had significant asbestos exposure with an average of 14.5 ± 2.4 insulator-years. The average subject had a mild restrictive ventilatory defect with the average total lung capacity and diffusion capacity 79% of predicted.

Metaplasia: Metaplasia was detectable in bronchial biopsies obtained from half of the study population. We attempted to relate smoking history and asbestos exposure history to the presence of metaplasia by separating the population into those with and without metaplasia and applying appropriate statistical tests. Smoking history was

associated with metaplasia because worse grades of metaplasia were seen in active smokers. Asbestos exposure history was not associated with metaplasia. We quantified free secretory component and keratins by micro ELISA. Free secretory component values for the population were similar to those of normal controls. Keratins were absent from normal controls and detectible in 54% of the asbestos workers. However, there was no relationship between keratins in bronchoalveolar lavage fluid and the presence of metaplasia detectible by bronchial biopsy. Finally, biopsy evidence of severe metaplasia was associated with the presence of acute inflammatory cells in lavage fluid. This persisted after stratification of the population by smoking status.

Fibrogenesis: From analysis of pulmonary function testing, we were able to divide the asbestos workers into those with evidence of functional derangement (DLCO < 80% of predicted) and those with relatively normal lung function. Subdivided this way, those with evidence of lung injury had a mean diffusion capacity 65% of predicted, whereas those with relatively normal lung function had diffusion capacities of 100% of predicted on average. The age, the approximate asbestos dose in insulator-years, and smoking history were similar in both groups. Asbestos workers with evidence of functional derangement had significantly more polymorphonuclear leukocytes recovered (8.6 ± $2x10^6$ neutrophils per BAL) than those without fibrogenesis (1.5 ± $0.5x10^6$). BAL neutrophil number correlated inversely with the diffusion capacity as a percent of predicted (R = -0.56). Those with evidence of lung injury had a significantly greater loss of diffusion capacity over time compared to those with relatively normal lungs. Stratification of the population by all possible demographic and functional variables yielded a useful predictive value for bronchoalveolar lavage data for "prediction" of functional deterioration.

Publications

Merrill WW, Carter DY, Cullen MR: The Relationship Between Bronchial Inflammatory Cells and Large Airway Metaplasia. Chest, in press, 1991

Merrill WW, Cullen MR, Carter D: Large Airway and Alveolar Space Inflammation as Predictors of Large Airway Metaplasia in Asbestos-Exposed Subjects. Presented, 4th Annual Congress on Lavage, Veruno, Italy, 1990. Respiration, in press, 1990

Merrill WW, Cullen M: Bronchoalveolar Lavage Neutrophils and Total Protein as Indices of Lung Injury in Asbestosis. Clin Res 37:474, 1989 (Abstract)

Merrill WW, Cullen M, Carter D, Marchandise FX: Histologic and Immunochemical Frequency of Metaplasia in Asbestos Workers. Am Rev Respir Dis 139:210, 1989 (Abstract)

Rankin JA, Marcy TA, Smith S, Olchowski J, Sussman J, Merrill WW: Human Airway Lining Fluid: Cellular and Protein Constituents. Am Rev Respir Dis 137:A5, 1988

Merrill WW, Cullen M, Cater D, Care SB, Mikes P: Histologic and Immunochemical Frequency of Bronchial Metaplasia in Smoking Asbestos Workers. Clin Res 35:536A, 1987

Marcy TW, Dorinsky PM, Davis WB, Merrill: Free Secretory Component and Keratins in Bronchoalveolar Lavage Fluid as Markers of Airway Epithelial Cell Injury in Bronchiolitis Obliterans. Am Rev Respir Dis 135:A409, 1987

Environmental Toxicity of Isocyanates

William E. Brown, Ph.D.
Carnegie-Mellon University
Department of Biological Sciences
4400 Fifth Avenue
Pittsburgh, Pennsylvania 15213-3890

Program Area: *Occupational Lung Diseases*
Grant Number: *5 R01 OH02214-03*
Start & End Dates: *02/01/87 - 06/30/90*
Funding Level: *$100,008 ($355,739 Cum)*

Importance to Occupational Safety and Health

Isocyanates are a group of highly reactive chemicals whose role in industrial synthesis continues to increase. Isocyanates are used for production of polyurethanes, rigid and flexible foams, and pesticides. Exposure to isocyanate vapors is a particular hazard for workers in occupations such as paint and coatings application, which require the use of the reactive form of the compound. Typical responses to isocyanates range from sensory irritation to chronic pulmonary disease. The identification of the specific *in vivo*

targets of inhaled isocyanates will enable development of appropriate radioimmunoassays for use in the analysis of blood or urine samples from workers to determine the extent of their exposure to isocyanates. The application of the exposure protocol used in these studies may provide new information to define different threshold events in the exposure to isocyanates. These include a true definition of the threshold for tissue damages, for sensitization, and for appearance of circulating modified macromolecules. Results of these studies will identify *in vivo* reactions of airborne isocyanates and provide methods for quantitative evaluation of isocyanate exposures. Conclusions drawn from these studies may be used to evaluate mechanisms involving exposure to reactive gases.

Objectives

The goal of the proposed research is to gain an understanding of the molecular events involved in the toxic responses to reactive gases in general, using isocyanates as model compounds. These responses include sensory and pulmonary irritation, sensitization, and chronic impairment of pulmonary function. The four specific aims are to identify *in vivo* sites of modification by inhaled isocyanates, to identify molecular markers related to exposure, to measure hydrolysis rates of isocyanates under normal atmospheric conditions, and to determine the specificity of isocyanates toward protein receptors.

Methodology

The measurement of the fate of inhaled isocyanates is being accomplished by exposing guinea pigs to atmospheres containing known concentrations of radioactively labeled isocyanates. Isocyanates being tested are toluene diisocyanate (TDI), hexamethylene diisocyanate (HDI), and methyl isocyanate (MIC). Tissues from the respiratory tract, as well as all other major organs and body fluids are collected following controlled exposures. The tissues are subjected to biochemical analysis using extraction, electrophoretic, immunochemical, and chromatographic methods, and to histological analysis using standard staining and autoradiographic techniques to identify the form and location of the radiolabel. The physiological fluids are similarly fractionated to analyze for soluble macromolecular targets as well as metabolic reaction products of isocyanates. The identification of specific reaction sites of isocyanates on protein targets are being analyzed using standard protein chemistry methods. *In vitro* labeled targets are being investigated in a similar manner after complete characterization of the specificity of reaction under defined conditions.

Significant Findings

Acute exposures were done at relatively low concentrations for short periods of time. Due to the cannulation procedure, it was possible to monitor the uptake of radioactivity into the bloodstream during exposure and to show that for all three isocyanates, some form of the radioactive compound entered the bloodstream within minutes and increased linearly during exposure. Another important finding of the blood analysis was that the radioactivity persisted in the bloodstream up to 2 weeks post-exposure at a constant level regardless of isocyanate tested or initial dose.

Once the isocyanate-exposed tissues and fluids were collected, the next stage of research involved the quantitation of radioactivity in the major tissues and fluids as a function of concentration, isocyanate tested, and time post-exposure. This analysis was performed to determine the primary target tissues and assess metabolic fate and clearance, in a general sense. From these studies, the airways were determined to be the primary target tissues. The fact that radioactivity was also found in tissues such as the liver, kidney, and spleen suggests the possibility of systemic delivery and effect of inhaled isocyanates.

Once the airway tissues were determined to be a primary target at the tissue level, histologic and autoradiographic analyses were performed to address the cellular distribution. The primary cellular target was found to be the respiratory epithelial cells and the subepithelial supporting structure. Co-localization with airway smooth muscle was also observed. This work is one of the first examples of the deposition of reactive gases, certainly for three structural variants of the same functional group.

Based on the localization pattern and airway responses which are typically associated with isocyanate exposure, several airway molecules were hypothesized to be modified by the isocyanates. Biochemical characterization of lung homogenates was performed to identify macromolecular targets. Laminin was identified as one such target primarily by immunochemical procedures. Preliminary *in vitro* studies have indicated that the structural modification of laminin by isocyanates does decrease its cell adhesion properties.

Another target molecule that has been determined is a 70 kDa protein. This protein has been shown in this work to be a common target for all three isocyanates and is the form of radioactivity which persists in the bloodstream. Through the

characterization of target molecules in the lung, another potentially important molecule was found. This small molecule is, however, not a direct target since it is not radioactively labeled, but it is related to isocyanate exposure and concentration. Examination of gel filtration HPLC profiles of lung extracts from exposures to all three isocyanates revealed this unique, dose-dependent, HPLC peak which did not contain radioactivity. Preliminary analysis of the material shows it to be approximately 2,000 molecular weight with an absorbance maximum at 254 nm.

Publications

Kennedy AL, Alarie Y, Brown WE: Comparative Analysis of the Uptake and Distribution of Inhaled ^{14}C-Labeled Isocyanates in Blood. The Toxicologist 10:236, 1990 (Abstract #943)

Kennedy AL, Wilson TR, Brown WE: Analysis of Functional Alterations of Laminin Modified by Isocyanates *In Vivo* and *In Vitro*. Amer Rev Resp Dis 141:A706, 1990

Kennedy AL, Stock MF, Alarie Y, Brown WE: Uptake and Distribution of ^{14}C During and Following Inhalation Exposure to Radioactive Toluene Diisocyanate. Toxicol Appl Pharmacol 100:280-292, 1989

Kennedy AL, Singh G, Brown WE: Isocyanate-Induced Injury and Labeling of Airway Epithelium. The FASEB Journal 3:A325, 1989 (Abstract #577)

Kennedy AL, Singh G, Brown WE: Modification of Airway Proteins and Induction of Secondary Responses by Inhalation Exposure to Isocyanates. Amer Rev Resp Dis 139:A387, 1989

Ferguson JS, Kennedy AL, Stock MF, Brown WE, Alarie Y: Uptake and Distribution of ^{14}C During and Following Exposure to Methyl Isocyanate. Toxicol Appl Pharmacol 94:104-117, 1988

Kennedy AL, Singh G, Brown WE: Localization and Purification of Labeled Lung Macromolecules Following Inhalation Exposure to Radioactive Isocyanates. Amer Rev Resp Dis 137:324, 1988

Alarie Y, Stock MF, Kennedy AL, Brown WE: Uptake in Blood of ^{14}C During and Following Exposure to [^{14}C] Methyl Isocyanate. Toxicologist 8:154, 1988 (Abstract #612)

Kennedy AL, Alarie Y, Brown WE: A Histological and Biochemical Analysis of the *In Vivo* Targets of Inhaled Radioactive Methyl Isocyanate. Toxicologist 8:154, 1988 (Abstract #613)

Kennedy AL, Brown WE: Differential Labeling of Blood Proteins by Isocyanates *In Vivo*. FASEB Journal 2:A569, 1988 (Abstract #1588)

Mechanism and Treatment of Phosgene Poisoning

Andrew J. Ghio, M.D.
Duke University Medical Center
Division of Allergy, Critical Care, and Respiratory Medicine
Box 3177
Durham, North Carolina 27710

Program Area: *Occupational Lung Diseases*
Grant Number: *5 R01 OH02264-05*
Start & End Dates: *09/30/88 – 09/29/90*
Funding Level: *$153,757 ($662,108 Cum)*

Importance to Occupational Safety and Health

Phosgene ($COCl_2$) is a toxic gas used commercially as a basic monomer in the synthesis of a wide variety of industrial agents. As a result of this wide application, the occupational risk of exposure is increased in the chemicals industry. In addition, transport of this extremely toxic substance through urban centers and use in chemical warfare place other populations at risk.

Objectives

In several forms of lung inhalation injury, the original causative agent or event produces chemotaxins that recruit polymorphonuclear leukocytes into the lung, resulting in magnification of injury. As a result of the association of lung neutrophils with phosgene inhalation, we tested the hypothesis that lung injury and mortality from phosgene was also associated with a LTB_4 directed influx of neutrophils.

Methodology

We employed murine models of phosgene lung injury. To study the role of neutrophils in lung injury and mortality after phosgene, we investigated

the effects of leukocyte depletion with cyclophosphamide, inhibiting the generation of the chemotaxin leukotriene B_4 by 5-lipoxygenase inhibitor AA861, and impairing neutrophil migration with the microtubular poison colchicine. Lavage protein, differentials, thiobarbituric acid reactive products, and lung function tests 24 hours after $COCl_2$ exposure were employed as indices of lung damage in Sprague-Dawley rats. Mortality of CD-1 mice was also used as an endpoint in the assessment of pharmacologic intervention.

Significant Findings

Cyclophosphamide, AA861, and colchicine injected before exposure significantly reduced lung damage in rats exposed to phosgene (0.5 ppm x 60 min.). Cyclophosphamide, AA861, and colchicine also significantly decreased mortality from phosgene (2.0 ppm x 90 min.) in mice. Colchicine significantly reduced neutrophil influx, lung injury, and mortality even when given 30 minutes after phosgene exposure. We conclude that lung injury and mortality after phosgene exposure are associated with an influx of neutrophils into the lung. Preventing neutrophil migration with colchicine may hold therapeutic potential in phosgene poisoning.

Publications

Ghio AJ, Kennedy TP, Schapira RM, Crumbliss AR, Hoidal JR: Hypothesis: Is Lung Disease After Silicate Inhalation Caused by Oxidant Generation? Lancet 336:967-969, 1990

Baser ME, Kennedy TP, Dodson R, et al.: Hydroxyl Radical Generating Activity of Hydrous but not Calcined Kaolin is Prevented by Surface Modification with Dipalmitoyl Lecithin. J Toxicol Environ Health, in press, 1989

Kennedy TP, Rao NV, et al.: The Role of Reactive Oxygen Species in Reperfusion Injury of the Rabbit Lung. J Clin Invest, in press, 1989

Kennedy TP, Dodson R, et al.: Dusts Causing Pneumoconiosis Generate ·OH and Produce Hemolysis by Acting as Fenton Catalysts. Archiv Biochem Biophys 269:359-364, 1989

Kennedy TP, Michael JR, Hoidal JR, et al.: Dibutyryl Cyclic AMP, Aminophylline and Beta Adrenergic Agonists Protect Against the Pulmonary Edema Caused by Phosgene. J Appl Physiol, in press, 1989

Kennedy TP, Gordon GB, et al.: Amiodarone Causes Acute Oxidant Lung Injury in Ventilated and Perfused Rabbit Lungs. J Cardiovasc Pharmacol 12:23-36, 1988

Influence of Particles on Occupational Lung Disease

David Warshawsky, Ph.D.
University of Cincinnati Medical Center
Department of Environmental Health
3223 Eden Avenue
Cincinnati, Ohio 45267-0056

Program Area: *Occupational Lung Diseases*
Grant Number: *1 R01 OH02277-01A2*
Start & End Dates: *09/30/89 – 03/31/93*
Funding Level: *$166,651 ($166,651 Cum)*

Importance to Occupational Safety and Health

Epidemiologic and experimental studies indicate that particles and/or chemical carcinogens are important in the development of respiratory disease. Occupational exposure to silica often includes exposure to polycyclic aromatic hydrocarbons (PAH); silica has an enhancing effect on benzo(a)pyrene induced lung carcinogenesis. This study is designed to investigate the ability of pulmonary alveolar macrophages (AM) to metabolize BaP-coated silica. In the evaluation of occupational hazards that may lead to increased susceptibility to lung cancer, the cocarcinogenic potential of an exposure is an important consideration. This research will provide information on particulate modified BaP metabolism and will contribute to our understanding of the involvement of pulmonary alveolar macrophage in the mechanism of lung disease.

Objectives

The long-term objective of this research is to investigate the role that AM play in the particulate-dependent response of the lung to BaP via mechanisms involving BaP metabolism. Although the mechanism of cocarcinogenic action is unknown, several investigators have implicated BaP metabolism. An important biological response to inhaled particles is ingestion by AM and clearance from the lung. Since these cells have the capacity to metabolize BaP, it is possible that altered BaP

metabolism leading to enhanced carcinogenic potential occurs in the AM following phagocytosis of silica particles and adsorbed BaP.

Methodology

Male Syrian Golden hamsters are known to be susceptible to the formation of lung tumors by BaP-coated particles. Alveolar macrophages (AM) were isolated by tracheal lavage from male Syrian hamsters (100-150 g, 8-9 wks old). The hamsters were anesthetized with sodium pentobarbital IP (0.5 ml 1% solution), and exsanguinated by cutting the abdominal aorta. The trachea was cannulated with a blunt 18 gauge needle and attached to a 3-way stopcock. The lungs were lavaged 8 times *in situ* with calcium and magnesium-free phosphate buffered saline (PBS pH = 7.2) at a volume equal to 4-5 ml. The total recovery of volume is about 90%. The fluid was placed in a 50 ml plastic centrifuge tube on ice. AMs were separated from the lavage fluid by centrifugation at the rate 200x g for 10 min. at room temperature. After the centrifugation, the supernatant was discarded and the pellets were resuspended with RPMI-1640 medium containing 0.1% gentamicin, 25 mM L-glutamine, 0.2% sodium bicarbonate and 2 mg/ml bovine serum albumin pH = 7.2). An aliquot of the cell suspension was removed to determine the viability and the numbers of cells by trypan blue staining procedure. Another aliquot of the cell suspension was used to identify the purity of AM by using cellular differential staining (Diff-Quik stain set Sci. Product Inc.). The population of alveolar macrophages for each isolation was about 90-95%. About $1x10^6$: cells with 2.5 ml RPMI-1640 were plated for each petri dish. After 1.5 hr, the unattached cells were removed. Then the cells were started with chemical treatments, ie. ferric oxide and Min-U-Sil silica. Viability analyses were carried out at 24- and 48-hr time points.

In future studies, the remainder of the medium will be extracted with ethyl acetate. The ethyl acetate extract will be analyzed by HPLC to quantitate metabolites and parent compound. The aqueous layer will be analyzed for the presence of conjugates. The AM will be removed and cells will be analyzed as described above. Additional studies will be conducted to compare the extent of binding to DNA and protein to the release of metabolites from the cell. The DNA and total protein will be isolated by the phenol extraction method. The extent of binding will be determined by liquid scintillation spectrometry.

In conjunction with the further studies, media from the AM will be extracted with ethyl acetate and evaporated to dryness. The residue will be reconstituted in a water methanol mixture and the parent compound will be separated from the metabolites by reverse phase Sep-pak chromatography. The metabolite mixture with and without BaP will then be analyzed by bacterial mutagenesis assays with and without S9.

Significant Findings

The comparative viability of the AM in the presence of ferric oxide and silica was undertaken to determine noncytotoxic doses during phagocytosis. Doses of ferric oxide and silica from 0.0 to 0.5 mg were used. The viability of the AM in the presence of ferric oxide up to the highest dose was similar to controls. After 24 and 48 hrs, the viability of the AM was approximately 80 and 70%, respectively. In the presence of silica, the viability of the AM was similar to controls up to 0.05 mg, approximately 80 and 70% at 24 and 48 hrs, respectively. At 0.1 mg silica, the viability of the AM began to drop to 40%, and at 0.5 mg, the viability was essentially zero. At the present time, similar studies are underway using other forms of silica and BaP coated particles in the presence of cytochrome C to monitor changes in the basal metabolic rate of the AM as a measure of phagocytosis.

The ferric oxide used was of respirable size with a particulate size distribution of greater than 90% having diameters less than 5 microns and over 70% having diameters less than 2.5 microns. The crystalline silica used was of respirable size with a particulate size distribution of greater than 99% having diameters less than 5 microns and over 90% having diameters less than 2.5 microns. The silica particles have a mean diameter of 0.83 microns and a surface area of 2.99 m^2/g. Work is in progress on particulate sizing of BaP coated forms of silica and ferric oxide. Metabolism studies of BaP and BaP coated particles are in progress. Additionally ^{32}P-postlabeling techniques have been developed to investigate the effects of particles on BaP adduct patterns of DNA in the alveolar macrophage.

Pilot Project to Assess Mortality Among Former Chromium Smelter Workers

Kenneth D. Rosenman, M.D.
Michigan State University
College of Human Medicine
Department of Medicine
B-220 Life Sciences Building
East Lansing, Michigan 48824-1317

Program Area: *Occupational Lung Diseases*
Grant Number: *5 R01 OH02298-02*
Start & End Dates: *07/01/89 - 06/30/91*
Funding Level: *$34,068 ($129,954 Cum)*

Importance to Occupational Safety and Health

This study will provide better estimates of the risk of lung cancer among chromium smelter workers. It will also provide data on the feasibility of contacting high risk workers and determining their willingness to participate in longitudinal followup research studies.

Objectives

1. To assess the mortality risk of employees involved in the production of chromate.
2. To assess the feasibility of conducting followup medical examinations to determine the predictive value of sister chromatid exchanges and chromosomal aberrations in a high risk population.

Methodology

Quarterly social security records were used to develop a cohort of former chromium smelter workers. Information on duration of employment was also obtained from these quarterly reports. Followup of the cohort has been made using Social Security records, the Internal Revenue Service letter forwarding service, and New Jersey Health Department death tapes. Further followup is planned using New Jersey motor vehicle records, the National Death Index, and a second mailing.

Significant Findings

A cohort of 5,300 former chromium smelter workers from five different plants was compiled. Approximately 2,000 individuals were identified as deceased, using social security records and the New Jersey death tapes. A letter and questionnaire were sent to approximately 1,200 former workers whose addresses could be located. About 750 returned the questionnaire. Fifty-five percent were interested in attending a medical screening.

Collection of death certificates and tracing of missing cohort members is currently underway.

Effect of Particle Load on Alveolar Clearance

Edward H. Bergofsky, M.D.
SUNY at Stony Brook
Pulmonary Medicine
HSC, T-17, Room 040
Stony Brook, New York 11794-8172

Program Area: *Occupational Lung Diseases*
Grant Number: *2 R01 OH02332-04*
Start & End Dates: *06/01/90 - 05/31/91*
Funding Level: *$163,262 ($569,878 Cum)*

Importance to Occupational Safety and Health

Respirable particulates in occupational and environmental aerosols deposit on mucus and respiratory membranes of the lung. Efficient clearance of these deposited particulates is necessary for normal lung function. Knowledge of normal clearance rate, route, and retention sites is necessary for understanding lung dosimetry and dysfunction when challenged by excessive numbers of particulates, cytotoxic or radioactive particles, or infectious organisms. Animal studies have indicated that increasing particle burdens in the lung depress the clearance rate and alter routes of clearance. In man, a number of studies suggest particle excess in the lung can lead to fibrotic lung disease, as well as other diseases. We have determined the normal rate and routes of clearance in a large animal, the sheep, whose lung size and anatomy is similar to man and can provide lung dosimetry in regard to sites of particle deposition, retention, and particle burden concentrations which may be directly applicable to man. The present study will examine the effect of increasing inhaled particle loads on subsequent clearance via our established sheep experimental model, and further elucidate the major mechanism whereby high loads of deposition damage lung defenses, impair particle clearance, and alter clearance routes.

Objectives

1. Determine alterations in normal particle clearance for supramicron (3.0 μm diameter) and submicron (0.5 μm diameter) particles under increasing lung burdens.
2. Quantitate the number of particles ingested by macrophages in the tracheobronchial tree in the first 48 hours post-deposition.
3. Quantitate the number of particles engulfed by alveolar macrophages over several months post-deposition and the clearance kinetics of these cells.
4. Examine the effects of particle loading on mobility and function capacity of macrophages such as Fc receptor proliferation, microbial killing, oxygen metabolites, and *in vitro* phagocytosis.

Methodology

Our approach will permit us to determine particle-cell ratio under low load for a supramicron and submicron particle. These particles will contain either a radioactive tag (^{57}Co) or a fluorescent tag. We will follow clearance non-invasively via gamma camera imagery and serial computer stored images. We will perform serial upper airway lavage and bronchoalveolar lavage. These cells will be examined for radioactivity by well counter and for particle content by fluorescent microscopy. The collected cells will be cultured and examined for Fc receptors by fluorescently tagged antibodies. Changes in functional characteristics, such as microbial killing, oxygen metabolites, and phagocytosis, will be investigated by a variety of *in vitro* assays. Increasing particle loads administered by instillation and inhalation followed by gamma imagery and serial lavage will be evaluated for alterations in clearance and cell functions as outlined above.

Significant Findings

1. Normal tracheobronchial clearance is complete in 45 hours and alveolar clearance has a half-life of 30 days for the 3.0 μm particle as determined by gamma camera imagery.
2. On instillation, 35% of the tracheobronchial macrophages contain both 0.5 μm particles and 3.0 μm particles at 1 hour post-deposition. The ratio of 0.5 μm particles to 3.0 μm particles engulfed by macrophages was the same as the number of particles deposited (400:1). No particles were found in tracheobronchial macrophages 48 hours post-deposition, indicating upper airway macrophages had cleared within 48 hours, confirming the non-invasive imagery of finding 1.
3. On instillation, 40% of the alveolar macrophages contained particles at 24 and 48 hours post-deposition with 12% containing >5 particles. By day 10, only 10% of the macrophages contained particles and only 1% had >5 particles. On inhalation, 10% of the alveolar macrophages contained particles at 24 and 48 hours post-inhalation with no macrophages containing >5 particles. By day 10, greater than 30% of the macrophages contained particles with 11% having >5 particles. By day 30, only 3% of the macrophages contained particles with no macrophages containing >5 particles. These findings suggest either macrophages are activated upon engulfing particles which subsequently render them more efficient in ingesting other particles or a subpopulation of cells exist *in situ* which react with non-immunogenic particulates.

Publications

Langenback EG, Bergofsky EH, Halpern JG, Foster WM: Determining Deposition Sites of Inhaled Lung Particles and Their Effect on Clearance. Journal of Applied Physiology 68(4):1427-1434, 1990

Langenback EG, Bergofsky EH, Halpern JG, Foster WM: Supramicron Sized Particle Clearance from Alveoli: Route and Kinetics. J Appl Physiol 69(4):1032-1308, 1990

Goldstein RA, Rohatgi PK, Bergofsky EH, et al.: Clinical Role of Bronchoalveolar Lavage in Adults with Pulmonary Disease. Am Rev Resp Dis 142:481-486, 1990

Langenback EG, Bergofsky EH, Halpern JG, Foster WM: The Sequestered State Prolongs Clearance of Particles from Alveoli. Am Rev Resp Dis 141:A525, 1990 (Abstract)

Langenback EG, Foster WM, Bergofsky EH: Calculating Concentration of Inhaled Radiolabeled Particles from External Gamma Counting: External Counting Efficiency and Attenuation Coefficient of Thorax. Journal of Toxicology and Environmental Health 27:139-152, 1989

Langenback EG, Bergofsky EH, Halpern JG, Foster WM: Determining Anatomic Deposition Sites of Inhaled Lung Particles and Their Effects on Subsequent Clearance. Am Rev Resp Dis 139:A246, 1989 (Abstract)

Silver JA, Groth ML, Bergofsky EH, Foster WM: Distribution of Regional Lung-Gas Volume vs. Pulmonary Tissue Attenuation in Humans: Effects of Lung Inhalation, Hydrostatic Pressure, and Chest Wall Tissue Density. Am Rev Resp Dis 139:A104, 1989 (Abstract)

Foster WM, Langenback EG, Bergofsky EH: Flow-limitation of Expiration Induces Central Particle Deposition and Disrupts Effective Flow of Airway Mucus. Ann Occup Hyg 32:101-111, 1988 (Supp)

Foster WM, Costa DL, Langenback EG: Ozone Exposure Alters Tracheobronchial Mucociliary Function in Man. J Appl Physiol 63:996-1002, 1987

Vitkun SA, Foster WM, Bergofsky EH, Poppers PJ: Bronchodilating Effects of Anesthetic Ketamine in an *In Vitro* Guinea Pig Preparation. Lung 165:101-13, 1987

Lung Disease in Chinese Textile Workers

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

Program Area: *Occupational Lung Diseases*
Grant Number: *1 R01 OH02421-01A1*
Start & End Dates: *06/01/88 - 12/31/89*
Funding Level: *$78,510 ($78,510 Cum)*

Importance to Occupational Safety and Health

This study is a longitudinal follow-up of cotton textile workers in Shanghai, China. The relevance of the knowledge gained from this work includes: the relative contributions of cotton dust and gram negative bacterial endotoxins in producing acute and chronic respiratory disease; the rate of annual decline in lung function after exposure to cotton dust; and the importance of acute, cross-shift change in FEV_1 in predicting longitudinal loss of lung function. Determination of exposure-response for gram negative bacterial endotoxins is important not only for textile workers, but also for thousands of workers exposed to other organic dusts and environments rich in endotoxin.

Objectives

Briefly stated, the project objectives have been:

1. To determine the 5-year incidence and remission of byssinosis and non-specific respiratory symptoms among cotton textile workers, using silk workers for comparison, and to relate these findings to exposure to cotton dust and endotoxin.
2. To determine the rate of annual decline in pulmonary function in cotton workers and silk referents and relate these outcomes to various estimates of current and historical work exposures.
3. To explore the relative contributions of cotton dust and airborne gram negative endotoxin exposure in the development and progression of respiratory symptoms and pulmonary function change.
4. To explore the assumption of a cross-shift change in FEV_1 at baseline screening and subsequent development of respiratory symptoms and loss of FEV_1.

Methodology

The study is a 5-year follow-up with surveys done at year 0 and year 5. Respiratory questionnaire, pulmonary function, and air sampling were performed at both surveys using identical techniques. Retirees were contacted and tested at year 5; and cause of death, as well as other reasons for loss from cohort, was ascertained on all subjects.

Significant Findings

Symptoms. Ninety percent of the original cohort was identified at the time of the 5-year survey. There were no significant differences in symptoms or baseline pulmonary function between those retested and those lost to follow-up. Cotton textile workers reported an excess of both acute and chronic symptoms as compared with silk workers, after adjustments for smoking. However, byssinosis incidence was very low: 4.2% of smokers and 2.7% of non-smokers. As with other longitudinal studies, there was considerable symptom variability between the two surveys. However, chronic respiratory symptoms (chronic bronchitis, chronic cough) and chest tightness at work were more common among cotton workers than silk workers. Dyspnea was a commonly reported symptom among both cotton and silk workers. Since it is a symptom generally associated with chronic respiratory impairment, its association with exposure and with initial survey results was examined.

Pulmonary Function. Over the 5-year period of study, cotton textile workers had a significantly greater loss in FEV_1 than silk workers (-203 mls vs. -170 mls, $p < 0.05$). This excess loss was seen in all smoking categories. Efforts at quantitative exposure-response relationships for dust and endotoxin were not successful, probably due to exposure misclassification. Nevertheless, when examined in an autoregressive model, exposure to cotton dust results in a significantly greater annual decline in FEV_1 after adjusting for age, sex, height, smoking, and baseline FEV_1.

Interestingly, across-shift change in FEV_1 in cotton workers was predictive of 5-year loss in FEV_1 after adjustments for age and smoking. This relationship had not been firmly established by previous studies of cotton textile workers.

Symptom-Pulmonary Function Relationships. Despite the variability in symptom reporting in the two surveys, there is evidence of a relationship between symptom prevalence and lung function loss. Workers who consistently reported symptoms of byssinosis or chronic bronchitis had the greatest decline in lung function, followed by those with inconsistent reports (i.e., on one of two surveys), and finally by those who consistently reported no symptoms. It would therefore appear that hidden in the "noise" of respiratory symptom prevalence is an actual measure of disease.

Publications

Olenchock SA, Christiani DC, Ye TT, Lu PL. Airborne Dust and Endotoxin Concentrations in Various Work Environments Within Two Cotton Textile Mills in the People's Republic of China. Biomedical and Environmental Sciences, in press, 1990

Airway Hyperreponsiveness Due to Cotton Bract Exposure

E. Neil Schachter, M.D.
Mount Sinai School of Medicine
One Gustave L. Levy Place
A24-30 Box 1232
New York, New York 10029-6574

Program Area: *Occupational Lung Diseases*
Grant Number: *5 R01 OH02593-02*
Start & End Dates: *09/01/89 – 08/31/91*
Funding Level: *$135,213 ($267,155 Cum)*

Importance to Occupational Safety and Health

Byssinosis remains a significant occupational health priority in the United States. Many textile workers exposed over several decades before the advent of the current environmental standards are at risk of impairment due to chronic airway disease. Younger workers are at a lower risk, but the current prevalence is unknown.

A growing body of evidence associates occupational and environmental pollutants with airway inflammation. The inflammation may be clinically reflected by non-specific airway hyperresponsiveness, a condition associated with the development of chronic airflow obstruction. By exploring the effects of cotton bract extract challenge on the development of airway responsiveness in our model of healthy volunteers, we hope to provide insight into the transition between the well-characterized acute response to cotton dust and the often irreversible chronic airflow obstruction found in many older workers with byssinosis. Additionally, this study will help validate our *in vivo* model of byssinosis in healthy volunteers exposed to cotton bract extract (CBE) and will extend our previous observations concerning the interaction of cigarette smoking and byssinosis.

Objectives

Our specific aims are:

1. To investigate if cotton bract exposure induces airway hyperresponsiveness in healthy smokers and non-smokers. The working hypothesis is that smokers have an asymptomatic, low-level of airway inflammation that makes them more susceptible to non-specific airway hyperresponsiveness following acute exposure to cotton bract extract (CBE).
2. To examine the effect of repeated CBE exposure on non-specific bronchial hyperresponsiveness. The working hypothesis is that repeated exposures to CBE leads to progressively greater inflammation in the airway which is reflected by airway hyperresponsiveness to methacholine (this despite the apparent tachyphylaxis that occurs with lung function changes over the work week).

Methodology

Our laboratory has developed an *in vivo* model for the effects of cotton dust on human airways. The model consists of studying lung function changes resulting from challenge with an aerosol

containing the water soluble extract of cotton bracts (CBE). The two major objectives of the current study will be examined using this model.

Objective 1: In 50 smokers and 25 non-smokers, challenge with CBE will be followed by a methacholine challenge test two hours after CBE exposure to look for differences between these groups.

Objective 2: The airway responses following a single CBE exposure will be compared to the effects after exposure for 5 continuous days and again following a two-day absence of exposure (e.g., a weekend). This will permit us to study cumulative effects of repeated exposures.

Significant Findings

We exposed 19 healthy non-smokers (NS) to CBE inhalation on 5 consecutive days, and on a 6th day, following a 2-day interruption of CBE inhalation. Partial and maximal expiratory flow volume loops were obtained prior to baseline (BL) and at 15-minute intervals for 2 hrs after CBE inhalation.

The average maximal MEF40 (P) percent decrement from BL (AMMPDB) was calculated for each of the 6 days; the AMMPDB for each day was 14.3 ± 3.4% on day 1, 9.2 ± 4.0% on day 2, 11.3 ± 3.8% on day 3, 8.7 ± 3.4% on day 4, 9.2 ± 3.5% on day 5, and 13.5 ± 3.6% on day 6. Longitudinal data analysis, comparing the AMMPDB from day 1 with the AMMPDB from each of the subsequent days revealed that the AMMPDB was greater on day 1 than on day 2 ($p = .11$), day 4 ($p < .05$) and day 5 ($p = .07$). No significant difference in AMMPDB was noted between day 1 and day 6 ($p = .76$). No significant difference in AMMPDBs was noted between non-Monday days. Conclusion: (1) acute decrements in expiratory flowrates were observed following sequential daily challenges with CBE of cotton bract extract; (2) daily decrements in expiratory flowrate following inhalation of CBE on 5 consecutive days were greatest on the first day; (3) after a 2-day interruption of CBE inhalation, CBE-induced decrements in expiratory flowrate return to levels noted on the first day of CBE inhalation.

We studied the response to methacholine challenge (MC) at baseline (BL) and 2 hrs. after the inhalation of nebulized CBE in 34 healthy smokers (HS) (mean = 11 pack years) and 20 healthy nonsmokers (HNS) ages 18-40. Partial and maximal expiratory flow volume loops were obtained prior to bronchial challenge (BL), at fifteen-minute intervals following CBE inhalation, and after each inhaled incremental dose of MC up to a maximal dose of 200 mg/ml.

In 4 of 20 HNS versus 18 of 34 HS ($p < .05$), a > 20% decrement in MEF20 (P) occurred within 2 hours of CBE inhalation. The mean BL MC log (PD20MEF40 (P)) +1 was significantly lower in smokers vs. non-smokers, 1.95 vs. 2.81 ($p < 0.001$). Two hours after CBE inhalation, no significant change in bronchial responsiveness to methacholine was noted in the HNS. However, in the HS a lower log (PD20MEF40 (P)) +1 for methacholine was noted after CBE challenge; 1.95 vs. 1.60 ($p = .07$). At 2 hours after CBE inhalation, the response to methacholine was lower in smokers vs. non-smokers ($p = 0.01$). Conclusion: (1) young HS have a higher response rate to CBE induced flow changes than HNS; (2) CBE enhances airway reactivity in HS; and (3) HS exhibit greater bronchial responsiveness than HNS to methacholine both at BL and 2 hrs after CBE inhalation.

Publications

Russomanno J, Siegel J, Witek TJ, Rienzi N, Zuskin E, Buck M, Schachter EN: Does Smoking Status Influence Responsiveness to Cotton Bract Extract? Proc Beltwide Cotton Conference, in press 1991

Witek TJ, Schachter EN: Problems in Respiratory Care Volume 3: 1 and 2: Current Issues in Respiratory Public Health. Volumes I and II, JB Lippincott, Philadelphia, 1990

Zuskin E, Kanceljak B, Witek TJ, Schachter EN: Acute Ventilatory Response to Green Coffee Dust Extract. Ann Allergy, in press, 1990

Zuskin E, Kanceljak B, Porkrajac D, Schachter EN, Witek TJ: Respiratory Symptoms and Lung Function in Hemp Workers. Br J Ind Med 47:627-632, 1990

Zuskin E, Ivankovic D, Schachter EN, Witek TJ: A Ten Year Follow-up Study of Cotton Textile Workers. Amer Rev Resp Dis, in press, 1990

Zuskin E, Kanceljak B, Schachter EN, Witek TJ, Marom Z, Goswami S, Maayani S: Immunological Changes in Soybean Workers. Int Arch of Occup Env Health, in press, 1990

Witek TJ, Schachter EN, Goldstein IF: Measurements of Lung Health Status in Environmental Epidemiology. In: Problems in Respiratory Care: Current Issues in Respiratory Public Health: II.,(eds. TJ Witek, EN Schachter), J.B. Lippincott 3:1-7, 1990

Witek TJ Jr., Schachter EN: Multidisciplinary Approaches to Environmental Lung Disease. Investigations in Byssinosis and Inner City Asthma. In: Current Issues in Respiratory Public Health, (eds. TJ Witek, Jr., EN Schachter), Philadelphia: JB Lippincott Co. 3:206-219, 1990

Zuskin E, Kanceljak B, Witek TJ, Schachter EN: Acute Effects of Herbal Tea Dust Extracts on Lung Function. Chest 96:1327-1231, 1989

A Rational Method for Sampling Airborne Fibrogenic Dust

Yehia Y. Hammad, D.Sc.
University of South Florida
College of Public Health
13301 Bruce B. Downs Boulevard
Tampa, Florida 33612

Program Area: *Occupational Lung Diseases*
Grant Number: *7 R01 OH02618-02*
Start & End Dates: *12/01/88 – 03/30/91*
Funding Level: *$77,608 ($169,561 Cum)*

Importance to Occupational Safety and Health

Current sampling instruments of respirable dust (RD) may overestimate the inhaled dose by up to 400% depending on the size distribution of the airborne dust. This limitation and the practice of assigning a single value for RD to all jobs regardless of the level of activity, i.e., respiratory frequency (RF) and tidal volume (TV), are incompatible with the advances in occupational epidemiology. Therefore, there is a need for a dust sampling instrument that is capable of estimating pulmonary deposition at various TV and RF.

Objectives

The objective of this project is to develop a new dust sampling device, designed to estimate pulmonary deposition (PD), to alleviate the limitations described above. The device consists of a 10 mm cyclone followed by a single-nozzle one-stage impactor. The dust fraction of interest is collected by impaction on a 10 mm diameter microscope cover slip. Estimation of PD is obtained by selecting the appropriate air flow rate and diameter of impactor so that the combined performance will simulate the bell shaped curves of PD at various RF and TV. Six single-nozzle impactors are used with jet diameters of 0.139, 0.159, 0.179, 0.198, 0.218, and 0.238 cm. This configuration was selected, rather than two impactors in series, to obtain better matching of PD (impactors have sharp and steep cut-off curves as compared to cyclones). A cyclone can also collect large amounts of dust without overloading. Other advantages of the instrument include improved estimation of the inhaled dose in epidemiologic studies of pneumoconiosis and reduced handling steps for chemical analysis of the collected dust, e.g., a silver membrane filter may be used as the collection stage for silica. This filter can be directly submitted for x-ray diffraction analysis. Performance of the new sampler is evaluated using aerosols with aerodynamic equivalent diameters ranging from 0.5 to 10 μm at air flow rates within the range of battery-operated personal sampling pumps (0.5 to 3.0 lpm).

Methodology

The aerosol is generated using a May Spinning Top Aerosol Generator. A Harvard syringe pump model 931 is used to feed the uranine-methylene blue (UMB) solution to the generator. Satellite aerosol is removed using a high volume EG&G Rotron blower model SL4P2. The generated aerosol is delivered to the top of a 21 ft^3 aerosol sampling chamber through a TSI Inc. Kr-85 particle neutralizer model 3054. The aerosol is thoroughly mixed with dilution air at the top of the chamber before it is allowed to pass through a diffusion screen to the sampling compartment of the chamber. The air is exhausted from the sampling compartment through another diffusion screen by the same EG&G blower. The UMB solution used in the experiment is produced by dissolving uranine and methylene blue in the ratio of 2:1 by weight in an aqueous solution of 40% ethyl alcohol. Particle size distributions are determined by microscopy and a density of 1.4 mg/cm^3 is assumed for the conversion of projected area diameters to aerodynamic equivalent diameters. Control of the size of the generated aerosols is achieved by the selection of the appropriate concentration of UMB used in the generation solution. A UV/VIS spectrophotometer is utilized for all UMB mass determinations.

Significant Findings

Because there are several types of membrane filters that can be used for aerosol sampling, it was decided to test the efficiency of aerosol recovery from three main types, i.e., MSA PVC, Nuclepore,

and Teflon. The results indicated that the PVC filters were associated with the highest recovery efficiency followed by the Nuclepore and Teflon. After normalizing recovery efficiencies to that of PVC, the obtained values were 100% for PVC with a coefficient of variation (CV) of 2.8%, 96.5% for Nuclepore with a CV of 3.9% and finally 88.9% for Teflon with a CV of 5.4%. Therefore, MSA PVC membrane filters are utilized in all experimental procedures.

Performance of the 10 mm nylon cyclone and two European types of metal cyclones utilized for personal sampling of respirable dust were also evaluated at air flow rates of 0.5, 0.75, 1, 1.5, 2 and 3 lpm. The penetration characteristics of the aluminum cyclones were consistently higher than those of the nylon version. The health implications of these findings, that is, overestimation of the inhaled dose, may be looked upon in two ways. The first case, utilization of these metal cyclones in epidemiologic investigations of pneumoconiosis will result in dose-response relationships that underestimate the toxicity of the agent. The second case is when dust sampling is performed for compliance purposes, where overestimation results in erring on the safe side, that is, protection of the workers' health.

Calibration of the 6 impactors indicates that their effective cut-off diameters are 1.61, 1.94, 2.32, 2.7, 3.12 and 3.56 um. The results obtained to date show that the basic concept of the proposed instrument is valid, and they also show that the combined performances of the impactors and cyclones at different air flow rates result in close simulation of pulmonary deposition at various ventilatory rates.

Publications

Hammad Y, Gomaa A: Evaluation of the Performance of the SKC Aluminum Respirable Dust Cyclone. Proc of 1990 American Industrial Hygiene Conference, Orlando, Florida, May 13-18, 1990

Silicosis and Pulmonary Cancer

David F. Goldsmith, Ph.D.
University of California
Division of Occupational and Environmental Medicine-ITEH
Department of Internal Medicine
Davis, California 95616

Program Area: *Occupational Lung Diseases*
Grant Number: *5 R01 OH02726-02*
Start & End Dates: *06/01/89 - 07/31/91*
Funding Level: *$156,525 ($300,972 Cum)*

Importance to Occupational Safety and Health

This study is a follow-up of historical files of the California Workers Compensation Appeals Board (WCAB). The files are claims for silicosis, pneumoconiosis, and other pulmonary conditions, and include twice the number of controls (including accidents, musculoskeletal injuries, and other claims). The pulmonary diseases claims plus controls comprise the California Silicosis Registry, which when complete will provide the first prospective capacity for epidemiologic studies of claims for silicosis and accidents. In addition, this research study will provide an examination of workers' compensation claims data.

Objectives

The registry was created to examine a contentious hypothesis in occupational cancer epidemiology: the association between silica exposure, silicosis, and cancer. In addition, the study will provide an opportunity to explore the relationship between silicosis, other pulmonary diseases, and mortality from tuberculosis and other nonmalignant respiratory diseases. Follow-up data from the controls will permit the examination of the mortality risks for claims related to accidents and other on-the-job conditions.

Methodology

Study follow-up will use NIOSH person-years program to calculate standardized mortality ratios (SMRs) for 89 causes of death. For cancers and other causes of death in excess, nested case-control studies will be undertaken that adjust for smoking (where available), other hazardous exposures, and drinking.

Significant Findings

Preliminary findings (using proportionate mortality ratios [PMRs]) demonstrate that WCAB claimants with silicosis have excess mortality ($p<0.05$) from tuberculosis, nonmalignant respiratory diseases, lung and pancreatic cancers. There were no excesses for gastric and lymphatic cancers, heart diseases, and accidents among lung disease claimants. Among controls, elevated PMRs ($p<0.05$) were found for several cancers including gastrointestinal and pulmonary neoplasms, and for suicide. There were deficits in risk for lung and heart diseases, accidents, and no deaths from tuberculosis.

Coal Dust Particle Size and Respiratory Disease

Thomas G. Robins, M.D., M.P.H.
The University of Michigan
School of Public Health
Occupational Health Program
1420 Washington Heights
Ann Arbor, Michigan 48109-2029

Program Area: *Occupational Lung Diseases*
Grant Number: *1 R01 OH02761-01*
Start & End Dates: *09/01/90 – 08/31/92*
Funding Level: *$120,257 ($120,257 Cum)*

Importance to Occupational Safety and Health

Exposure to coal mine dust is strongly associated with the development of coal workers' pneumoconiosis (CWP) and chronic obstructive lung disease, including emphysema and chronic bronchitis. The most important studies which demonstrate such effects use measurements of respirable coal mine dust, i.e., dust depositing primarily in the terminal airways and alveoli, as the basis of their exposure assessment. There are, however, good reasons to believe that some of the effects associated with coal dust, e.g., chronic cough and phlegm production, may be more specifically related to large particle-size dust which deposits primarily in the tracheo-bronchial tree. This study will characterize the particle-size distribution of underground coal mining occupations and use this information, in conjunction with previously developed respirable dust exposure estimates, to estimate exposures to dust depositing in the tracheobronchus. Exposure-response functions will then be fitted for a cohort of underground miners to determine the importance of tracheo-bronchial vs. respirable dust fractions in the etiology of lung diseases in miners. The results may help characterize the exposure-response function for respiratory disease in coal miners and more specifically determine the specific parameters of exposure that give rise to the observed effects.

Objectives

1. Characterize the particle-size distribution of dusts in underground coal mining operations.
2. Develop estimates of tracheo-bronchial dust exposures for a cohort of miners using previously developed respirable dust exposure estimates and the particle-size information.
3. Explore the exposure response functions for respirable and tracheobronchial dust exposures and the development of airflow limitations and symptoms of chronic bronchitis.

Methodology

Particle-size distributions of dust exposures will be characterized for a set of occupations derived from the work histories of miners participating in the National Study of Coal Workers' Pneumoconiosis. Several mines will be visited and exposures to miners employed in the targeted occupations will be monitored using a personal multi-stage impaction sampling device. Using a deposition model for pulmonary aerosols, the ratio of respirable to tracheo-bronchial dust will be calculated for each occupation. These ratios will then be applied to the respirable dust concentration data previously estimated from government sampling programs to develop several measures of dust exposure. Temporal aspects such as latency and exposure intensity will be considered in developing alternative parameters of cumulative exposure. Exposure response functions will then be fitted for each of the alternative exposure parameters with pulmonary function decrements and the development of symptoms of chronic bronchitis. The fit of the alternate models will be interpreted, where possible, to distinguish between alternative hypotheses concerning the mechanism of dust-induced injury and the development of lung abnormalities.

Significant Findings

None to date.

Detecting Lung Overload by Magnetometry

Sidney C. Soderholm, Ph.D.
University of Rochester
School of Medicine and Dentistry
Environmental Health Sciences Center
575 Elmwood Avenue, Box EHSC
Rochester, New York 14642

Program Area: *Occupational Lung Diseases*
Grant Number: *1 R01 OH02772-01*
Start & End Dates: *09/01/90 - 08/31/94*
Funding Level: *$210,090 ($210,090 Cum)*

Importance to Occupational Safety and Health

Rats chronically exposed to high concentrations of a variety of insoluble dusts develop lung overload in which particle clearance, i.e., the lungs' normal ability to remove deposited dust, is impaired. If exposure continues, pathological conditions develop which may be similar to the pneumoconioses which sometimes occur in workers after long-term exposures to high concentrations of dust. Extrapolation of data from rats suggests 1 to 3 grams of dust in human lungs might lead to significant impairment of particle clearance followed by disease if exposure continues. Projections indicate that current governmental limits on occupational dust concentrations may allow the mass of dust in workers' lungs to reach 1 gram in as little as 6 months of exposure.

Non-invasive measurement of fields produced by magnetic particles in lungs can characterize a number of functional parameters related to lung overload. Magnetometry has been used to measure burdens and clearance rates of inhaled magnetic particles in humans and experimental animals and to characterize macrophage mobility and cytoplasmic viscosity. Characterizing these functions and determining the dose of inhaled dust required to change them in workers and experimental animals would allow detailed comparisons among species to detect similarities and differences in disease states. These characterizations would also increase the level of confidence with which predictions of adverse effects in humans could be made from extrapolations of data obtained using experimental animals. Success in this project and planned subsequent human studies will lead to a better understanding of whether lung overload occurs in humans and how to set exposure guidelines to avoid adverse health effects in workers.

Objectives

The long-term objectives of the proposed line of research are to more fully characterize lung overload in rodents and to develop and apply methods for determining whether it occurs in humans. The overall aims of this project are to: (1) develop a magnetic test aerosol and assemble a magnetometry system suitable for measurements in rodents, (2) demonstrate that dust clearance rates can be measured reliably using magnetic aerosols, (3) test hypotheses which suggest magnetometry may have unique capabilities to detect and characterize lung overload, and (4) compare results from guinea pigs and rats to provide a broader information base for extrapolating to humans and for planning future human studies.

Methodology

Small groups of animals will be exposed for 13 weeks to different amounts of a magnetic dust and an "inert" dust (TiO_2). The degree of overload will be characterized by the clearance of radioactive tracer particles and by limited histology. Magnetometry will provide measurements of the lung burden of magnetic particles, lung clearance rates, macrophage mobility, and viscosity of the particle microenvironment. Changes in these parameters with degree of overload by the magnetic dust or TiO_2 (with a small amount of magnetic dust to allow magnetometry) will allow determination of which functional parameters are most useful in detecting lung overload. Changes in these parameters with other experimental variables will allow determination of whether confounding factors related to species, animal age, length of time since exposure to the magnetic dust, or length of time since exposure to the nonmagnetic dust might complicate the interpretation of the results of similar measurements in humans.

Significant Findings

None to date.

Pharmacomechanical Hyperresponsiveness in Ozone-Induced Airway Injury

Christopher G. Murlas, M.D.
Rush-Presbyterian St. Luke Medical Center
Department of Medicine
1653 W. Congress Parkway
Chicago, Illinois 60612

Program Area: *Occupational Lung Diseases*
Grant Number: *5 K01 OH00060-02*
Start & End Dates: *03/01/88 – 02/28/92*
Funding Level: *$32,400 ($64,800 Cum)*

Importance to Occupational Safety and Health

Our current research aims are to determine *in vivo* and *in vitro* mechanisms which increase airway muscarinic responsiveness. This has and will continue to be done in subjects with bronchial hyperreactivity, the increased airway irritability which characterizes asthma and ozone-induced lung injury. What we have learned from our previous studies of airway structure and function in this disorder suggests that injury to normal lung constituents results in the elaboration of factors leading to cholinergic neuromuscular hyperresponsiveness. Among the many potential cell types that could influence bronchomotor tone are cells of the respiratory mucosa which may affect airway muscle both pre- and post-synaptically. From our work, it appears that airway muscle responsiveness in acute, ozone-induced bronchial hyperreactivity is increased, and that this hyperresponsiveness is linked to more than one noncyclooxygenase, mucosa-derived factor in the guinea pig. Thus, we speculate that the hyperreactivity developing acutely after ozone exposure may be due to mucosa-derived factors which increase the responsiveness of airway muscle. Identification of these factors and the cellular mechanisms by which they augment smooth muscle contractility merit further study.

Objectives

Increased bronchial irritability (bronchial hyperreactivity) is a characteristic feature of asthma, and understanding its pathogenesis may provide new insights for better treatment. In guinea pigs with acute O_3-induced airway injury, we have found cholinergic hyperreactivity which may be related to a lipooxygenase product, possibly leukotriene, elaboration. Our recent studies have suggested that intralobar bronchial and tracheal muscle, from ozone-exposed airways, is hyperresponsive to ACh and KCl *in vitro*. We now aim to: (1) confirm whether or not the *in vitro* responsiveness of certain airway generations is increased in animals with ozone-induced bronchial hyperreactivity, (2) evaluate whether this responsiveness is specific or nonspecific, and (3) assess possible mechanisms for this effect, including airway cell neutral endopeptidase inactivation.

Methodology

To accomplish Aim 1, we will compare the effect of ozone- and sham-exposure *in vivo* on (a) smooth muscle preparations from different airway generations and on (b) airway muscle muscarinic responsiveness to endogenously released (via electrical field stimulation (EFS)) versus exogenous ACh. If ozone exposure augments EFS responsiveness, its possible pre-synaptic effects will be more directly assessed by measuring [^{3}H] ACh release from intramural cholinergic nerve terminals of airways. To further satisfy Aims 2 and 3, potential post-synaptic effects will be assessed, including the effects of oxidation on airway mucosal cell neutral endopeptidase.

Significant Findings

In this work, we speculated that acute, ozone-induced hyperreactivity may be related to airway mucosal cell injury which increases neuromuscular responsiveness. The biochemical events upon mucosal oxidant injury which are responsible for this pathophysiology are not well understood at present. Consequently, we investigated the effects of ozone exposure (3.0 ppm, 2h) on airway neutral endopeptidase (NEP) activity and bronchial reactivity to substance P in guinea pigs. Reactivity after ozone or air exposure was determined by measuring specific airway resistance in intact, unanesthetized, spontaneously breathing animals in response to increasing doses of intravenous substance P boluses. NEP activity was measured in tracheal homogenates made from each animal of other groups exposed to either ozone or room air. Using reverse phase high pressure liquid chromatography, this activity was characterized by the generation of phosphoramidon inhibitable product cleaved from succinyl-(ala)3-p-nitroaniline in the presence of 100 μM amastatin. We found that phosphoramidon significantly increased substance P reactivity in the air-exposed animals, but it had no effect in the ozone-exposed group.

This finding was associated with a significant reduction in NEP activity in ozone-exposed animals compared to the controls. In addition, those animals exposed to ozone showed airway muscle hyperresponsiveness *in vitro*. The smooth muscle of mucosa-intact airways from guinea pigs with ozone-induced bronchial hyperreacitvity was hyperresponsive *in vitro* to substance P and ACh, but not to KCl. Our data suggest that smooth muscle responsiveness is increased in guinea pigs with ozone-induced bronchial hyperreactivity, and that this hyperresponsiveness is linked to more than one noncyclooxygenase, mucosa-derived factor.

Both hypochlorous acid (HOCl) and hydrogen peroxide (H_2O_2) may be generated during oxidant airway injury. Consequently, we have investigated whether exposure of the airway mucosa *in vitro* to either of these agents caused an augmentation in airway muscle (ASM) responsiveness. We investigated whether exposure of guinea pig tracheal tissue to hypochlorous acid (HOCl) or hydrogen peroxide (H_2O_2) by perfusion through the airway lumen affected the responsiveness of airway muscle to ACh, KCl, or substance P in the presence or absence of 1 μM phosphoramidon, an inhibitor of neutral endopeptidase (NEP). We found that smooth muscle of mucosa-intact guinea pig airways perfused with HOCl, but not H_2O_2, was hyperresponsive to substance P, but not to ACh or KCl. Our results suggest that the smooth muscle hyperresponsiveness to substance P caused by airway perfusion with HOCl is produced by HOCl inactivation of mucosal NEP.

Airway mucosal cells may be a rich source of metalloendopeptidase. A variety of bronchoactive peptides are catabolized by neutral endopeptidase (NEP), an ectoenzyme expressed by respiratory mucosal cells. To pursue possible subcellular mechanisms for the influence of HOCl on airway mucosal cells, we assessed effects of HOCl exposure on NEP activity expressed by a human bronchial epithelial cell line (HBEC). We concluded that HOCl exposure decreases activity of HBEC plasma membrane NEP, but not of the cytosolic component. This loss appears to occur by oxidative inactivation of cell membrane NEP from which cells can be protected by reducing agent pretreatment.

Because of its potential pathophysiological importance, we have also examined whether the lysosomal hydrolase NAGA was elaborated in the airways of animals with ozone-induced hyperreactivity. We concluded that ozone-induced airway hyperreactivity in the guinea pig is associated with the presence of increased NAGA in bronchoalveolar fluid. Our data suggest that bronchoalveolar cells may be responsible for secretion of this enzyme into the airways after ozone exposure.

Publications

Lang Z, Murlas CG: HOCl Exposure of Human Bronchial Epithelial Cells Inactivates Plasma Membrane Neutral Endopeptidase. Am Rev Resp Dis, in press. Submitted for presentation at meetings of American Thoracic Society in Anaheim, CA, May 1991

Chodimella V, Skidgel R, Krowiak E, Murlas CG: Lung Peptidases, Including Carboxypeptidase, Modulate Airway Reactivity to Intravenous Bradyskinin. Am Rev Resp Dis, in press. Submitted for presentation at meetings of American Thoracic Society in Anaheim, CA, 1991

Murlas CG, Williams GJ, Lang Z, Chodimella V: Aerosolized Neutral Endopeptidase (NEP) Reverses the Increased Airway Reactivity to Substance P Caused by Ozone. Am Rev Resp Dis 141:A734, 1990. Presented at meetings of American Thoracic Society, Boston, MA, May 1990

Murlas CG: Environmental Airway of Mucosal and Changes in Hyperreactivity. In the Airway Epithelium: Structure and Function in Health and Disease, (eds. S Farmer, D Hay), Marcel Decker, Inc., pp 256-281, 1990

Murlas CG, Murphy TP, Lang Z: HOCl causes Airway Substance P Hyperresponsiveness and Neutral Endopeptidase (NEP) Hyporeactivity. Am J Physiol 258:L361-368, 1990

Steinberg DR, Bernstein DI, Bernstein IL, Murlas CG: Histaminic Hyperactivity after the Immediate Allergic Response. In: Year Book of Pulmonary Disease, (ed. GM Green), Year Book Medical Pub., Chicago IL, 1990

Murlas CG, Murphy T, Chodimella V: O_3-induced, Mucosa-Linked Airway Muscle Hyperresponsiveness in the Guinea Pig. J Appl Physiol 690:7-13, 1990

Rogness A, Murphy T, Davis S, Murlas CG: Exposure of Airway Mucosa to HOCl, but not H_2O_2, Increases Airway Muscle Responsiveness *In Vitro*. Am Rev Resp Dis 139:A616, 1989

Lee HK, Murlas CG: Electromechanical Effects of Leukotriene D_4 on Ferret Tracheal Muscle and its Muscarinic Responsiveness. Lung 167:173-185, 1989

Steinberg DR, Bernstein DI, Bernstein IL, Murlas CG: Prednisone Pretreatment Leads to Histaminic Airway Hyperreactivity Soon after Resolution of the Immediate Allergic Response. Chest 95:314-319, 1989

Murlas CG, Doupnik CA: Electromechanical Coupling of Ferret Airway Smooth Muscle in Response to Leukotriene C4. J Appl Physiol 66:2533-2538, 1989

Lang Z, Soskel N, Williams G, Murlas CG: Identification of Metalloendopeptidase Activity in Bovine Airway Mucosal Cells and Its Inhibition by Hypochlorous Acid. Am Rev Respir Dis 139:A236, 1989. Presented at meetings of American Thoracic Society, Cincinnati, OH, May 1989

Lew B, Davis S, Chodimella V, Murlas CG: Guinea Pig O_3-Induced Airway Hyperreactivity is Associated with Increased Airway Reactivity to Substance P Caused by Ozone. (Abstract)

Lee HK, Murlas CG: Electromechanical Responsiveness of Ferret Airway Smooth Muscle (ASM) to Leukotriene D4 (LTD4). Am Rev Respir Dis 137:A307, 1988. Presented at the meetings of American Thoracic Society, Las Vegas, NV, May, 1988 (Abstract)

Cibulas W, Brooks SM, Murlas CG, Miller ML, McKay RT: Toluene Diisocyanate-Induced Airway Hyperreactivity Occurs in Guinea Pigs Depleted of Granulocytes. J Appl Physiol 64:1773-1778, 1988

Murlas CG: Pathogenesis of Airway Hyperreactivity. Chest 93:1278-1282, 1988

Inhaled Toxic Agents: An Evaluation of Dose

Linda M. Hanna, Ph.D.
The Johns Hopkins University
School of Hygiene and Public Health
Department of Environmental Health Sciences
615 North Wolfe Street
Baltimore, Maryland 21205

Program Area: *Occupational Lung Diseases*
Grant Number: *5 K01 OH00067-03*
Start & End Dates: *07/01/87 - 12/31/90*
Funding Level: *$29,956 ($94,756 Cum)*

Importance to Occupational Safety and Health

The characterization of the risk upon exposure to an inhaled agent is based on the dose-response relationship between the agent and the respiratory tract. The evaluation of the dose-response relationship follows from the evaluation of the exposure-dose relationship. This association is relatively unknown because of the inaccessibility of the respiratory tract to measurement.

Objectives

The exposure-dose relationship during respiratory exposures was evaluated by a deterministic mathematical model of the mass transport process of respiratory gas absorption. The model includes physico-chemical properties of gases, such that the model is applicable to any gas/vapor for which these properties are known. In addition, the variability in regional dose as a function of physiologic and morphometric parameters was evaluated both from a theoretical viewpoint and empirical analysis.

Methodology

To assess target tissue dose, we developed a mathematical model, based on the principles of mass transport, to predict the mass flux and airstream concentrations of soluble pollutant gases/vapors as a function of distance into the respiratory system. The mathematical model is a generalized model capable of predicting respiratory absorption of gases/vapors of differing physico-chemical properties which may be applied to all animal species. Thus, species extrapolation of the exposure-dose relationship may be performed

utilizing this model. Because upper airway morphometry and airphase scrubbing efficiency (the convective mass transport coefficient) are two parameters of the gas absorption process, we are developing a method to use either MRI Scans or CT Scans, in conjunction with an image analyzer to evaluate upper airway morphometry and the variability of airway morphometry within a subject population for use in the mathematical model. Also under development is a method to evaluate convective mass transport coefficients using fluorescence spectroscopy. The coefficients are to be evaluated from the rate of naphthalene sublimation from the surface of a physical model of the upper airways to be constructed from the scans.

Significant Findings

Prior to this study, nasal morphometry has been characterized by perimeter and cross-sectional area. We have developed a new technique to evaluate nasal morphometry in living humans as measured from computed tomography scans (CT). The technique considers the nasal cavity as consisting of a possible three pathways. The pathways, in cross-section, are the regions surrounding each turbinate. The equivalent geometry of this region is either an annulus or a rectangular duct. These studies have provided parameters to compare upper airway geometry by determining the pathway width and area as measures of size, and the height-to-width ratio as a measure of shape. Based on measurements taken from a single cadaver included in this study, the pathway width of the cadaver inferior region ($x=4.05\pm.21$ mm, $n=6$) was significantly greater than those of living subjects ($x=2.88\pm.76$ mm, $n=24$). These differences suggest postmortem shrinkage or distortion of the turbinate. In further evaluation of airway resistance (beyond the ostium internum) based on these measurements, it was predicted that a maximum of 70% of the flow would move through the inferior region of living subjects, while in the cadaver the flow would peak at 90%, which may have implications for mass transport studies performed in cadaver casted models. We are continuing to develop the technique to include evaluation of the three-dimensional image reconstruction of the CT scans. The technique will be used to evaluate morphometric variability in a subgroup of the population. In addition, we have compared the use of CT scans and MRI scans in evaluating airway morphometry. We have scanned a phantom, a living subject, and cadaver using both of these modalities. The major difference using these two modalities was in the three dimensional reconstruction in which the MRI scans provided less detail.

The dependence of the fraction of the gas penetrating the upper airway, f_p, on the route of breathing was evaluated using the mathematical model. The influence of the route of breathing and cavity dimensions on f_p was dependent on gas solubility. In the case of the moderately soluble gas, SO_2, nasal cavity dimensions over the range found in the morphometric analysis altered f_p at a resting ventilation rate (9.6 l/min) from 0.35 at the smallest dimensions to 0.05 at the largest, most likely due to the increase in residence time and surface area. At the same ventilation rate, the oral cavity was predicted to be the least efficient scrubber reaching 0.55 at the largest dimensions. The f_p of ozone, a less soluble gas, was most sensitive to the pseudo-first order reaction rate constant. In comparing nasal to oral breathing, the difference at a ventilation rate of 6 l/min was not very large (<0.1) and is nearly zero at 30 l/min and small reaction rate constants (k_{rx} = 1,500 or 5,000). The model also predicted that oronasal breathing was more efficient in scrubbing the inspired air than either nasal or oral breathing alone.

A fluorescence spectroscopy technique has also been developed to evaluate the convective mass transport coefficients within the upper airway. We have found the technique to determine the coefficients in a straight tube to be <30% of those predicted by theory. The difference between theory and measurements are typically within 25%. To be assured of precise measurements, we have been refining the method to establish the relationship between the photomultiplier voltage output and naphthalene concentration. Once the system is calibrated, we will perform measures of the coefficients in human nasal cavity models. To do so, we are developing a method to transfer the 3-D image reconstruction of the CT scans of living subjects to a CAD-CAMM system. This work will represent the first generation of a model based on the upper airway morphometry *in vivo*.

Publications

Hanna LM, Scherer PW, Frank R: Absorption of Soluble Gases and Vapors in the Respiratory System. In: Respiratory Physiology: An Analytical Approach. (eds. Chang HK, Paiva M), in press, 1989

The Immunopathogenesis of Occupational Diseases Due to Reactive Chemicals

David I. Bernstein, M.D.
University of Cincinnati Medical Center
Division of Immunology
231 Bethesda Avenue, M.L. 563
Cincinnati, Ohio 45267-0563

Program Area: *Occupational Lung Diseases*
Grant Number: *5 K01 OH00073-02*
Start & End Dates: *09/30/88 - 09/29/91*
Funding Level: *$32,400 ($64,800 Cum)*

Importance to Occupational Safety and Health

Reactive small molecular weight chemicals are recognized as important causes of occupational asthma and reactive airways disease. Occupational asthma has been associated with exposure to various types of chemical diisocyanates including toluene diisocyanate (TDI), diphenylmethane diisocyanate (MDI), and hexamethylene diisocyanate (HDI). It has been estimated that occupational asthma occurs in 5% of diisocyanate-exposed workers. The clinical presentations of diisocyanate asthma resemble other forms of immunologic asthma. However, specific IgE responses to relevant diisocyanate-human serum albumin (HSA) antigens have been identified in only 10% of symptomatic workers. As a result, other non-immunologic mechanisms have been postulated. A prior study showed that most workers with TDI asthma exhibited *in vitro* cellular responses after stimulation with specific TDI-HSA antigens, suggesting that cellular immunity may play a significant pathogenic role. Thus, it was postulated that specific *in vivo* cellular immune responses to diisocyanates in sensitized workers could result in production of cytokine mediators that could activate responder cell populations, (i.e., basophils, mast cells) to release bioactive mediators (i.e., histamine). Refinement of *in vivo* laboratory methods that measure cellular responses to specific occupational antigens could allow development of assays which could identify symptomatic workers or workers at potential risk for development of occupational immunologic disease. These results would possibly be more sensitive than currently available *in vitro* methods that measure specific IgG and IgE responses to these chemical antigens.

Objectives

The first objective of this proposal was to define whether specific cell-mediated immune responses could be detected in workers with occupational asthma. This question was to be studied in workers identified with occupational asthma resulting from exposure and sensitization to MDI.

The second objective of this study was to determine whether lymphocyte populations obtained from workers with occupational asthma produce histamine releasing factors (HRF) after specific *in vitro* stimulation with diisocyanate-HSA antigens. The overall hypothesis of this study is that cellular immunity may play a central role in the elicitation of occupational immunologic disease and that *in vitro* detection of such responses could serve as useful and sensitive markers of occupational immunologic lung disease.

Methodology

The population proposed to be studied comprised 20 workers with exposure to MDI, of which 10 had been diagnosed with occupational asthma and 10 had been asymptomatic with no respiratory complaints. Relevant test antigens were prepared by coupling MDI, HDI, and TDI to HSA followed by complete chemical characterization of resultant conjugates. The MDI-exposed population was evaluated by intracutaneous and epicutaneous testing to MDI-HSA, TDI-HSA, and HDI-HSA. To detect specific humoral immune responses, serum samples were assayed with specific IgG (ELISA) and specific IgE (RAST) to MDI-HSA. A panel of *in vitro* cellular assays was performed in study subjects which included: (1) direct leukocyte inhibitory factor (LIF) assay in response to HSA conjugates of TDI, MDI, and HDI; and (2) an assay for histamine releasing factor (HRF) derived from supernatants of 18-hour lymphocyte cell cultures after stimulation with relevant occupational antigens.

Significant Findings

During the first two years of this project, 11 diisocyanate workers have been recruited for the study. The latter individuals presented with prior histories of wheezing and dyspnea temporally related to MDI exposure. Challenge tests to MDI were able to be performed in 8 subjects, of which 5 were found to be positive. Of 11 workers studied, significant histamine releasing factor activity in response to diisocyanate HSA conjugates was noted in 4 workers. In all 4 workers who exhibited significant HRF activity, cross sensitivity to other

diisocyanate-HSA antigens was demonstrated. It was noteworthy that 3 of 4 subjects exhibiting significant HRF activity had positive specific provocation tests to diisocyanates. A leukocyte inhibitory factor assay was performed in all 11 workers who reported symptoms. Five workers exhibited significant inhibitory responses in response to diisocyanate HSA antigens. Among 6 subjects in whom results were evaluable for the both LIF and HRF assays, 3 exhibited concordance (positive responses to both assays) and 3 had discordant results. *In vivo* skin testing performed with HSA conjugates of TDI, MDI, and HDI were negative in all subjects. Serum specific IgE to MDI, TDI, and HDI-HSA was not detected. Elevations in specific IgG to diisocyanate HSA by the ELISA assay was detected in only 3 of 11 subjects, and there was no apparent relationship between specific antibody responses and positive responses to diisocyanate antigens in LIF and HRF assays.

Thus, the data indicate that histamine releasing factor (HRF) activity in response to specific antigens could be identified in 3 of 4 individuals with positive challenge tests. Further studies of this nature are planned in the final year of this grant to investigate HRF, LIF, and specific humoral responses in 10 asymptomatic-exposed MDI workers.

Effects of Zinc Oxide Welding Fume Inhalation

Paul D. Blanc, M.D.
University of California
School of Medicine
Division of Occupational and
Environmental Medicine
P.O. Box 0924
San Francisco, California 94143-0924

Program Area: *Occupational Lung Diseases*
Grant Number: *1 K01 OH00079-01A1*
Start & End Dates: *09/28/90 - 09/27/93*
Funding Level: *$53,920 ($53,920 Cum)*

Importance to Occupational Safety and Health

Physicians have long been aware of a self-limited syndrome of systemic illness associated with zinc oxide (ZnO_2) fume inhalation. This syndrome consists of a constellation of signs and symptoms suggesting a flu-like illness: malaise, myalgia, and fevers in the range of 38 to 39 degrees. This syndrome is marked by an abrupt onset after a latency of 6 - 24 hours following the inhalation of ZnO_2 particles in the respirable range (< 5 microns), typically ZnO_2 fume freshly generated through welding galvanized metals or melting brass. This zinc-associated flu-like illness continues for 24 to 48 hours and then spontaneously remits. The syndrome has received many acronyms from both medical practitioners and the lay public most familiar with the illness, particularly from welders and brass founders. These names include: metal fume fever (MFF), brass chills, spelter shakes, and zinc ague. In 1975, NIOSH estimated that 50,000 workers were potentially exposed to ZnO_2, including fume (such as in welding and foundry operations) and non-fume (such as in pigments).

The mechanisms underlying zinc-induced MFF are unknown. Various researchers have hypothesized that zinc may cause cytotoxic protein release, induce immunologic phenomena, or directly catalyze enzymatic reactions. The hypothesis of this study is novel, proposing that the effects of ZnO_2 fume inhalation are mediated by cytokines. Bronchoalveolar lavage (BAL) analysis of humans exposed to zinc fume will provide the data critical to identifying the mechanism of ZnO_2 inhalation effects on the cellular and biochemical level. This study will delineate the dose-response relationship between ZnO_2 exposure and human health effects to a much more precise degree than currently known, providing data crucial to evaluating currently promulgated safety standards as well as assessing the health effects of real world conditions where higher exposures are frequent. This study addresses MFF, an occupational illness that is a significant cause of morbidity in its own right. Yet ZnO_2 MFF is only one of a variety of exposure related systemic febrile syndromes. This study will develop approaches that can later be applied generally to these occupational conditions.

Objectives

Inhalation of ZnO_2 fume causes a syndrome consisting of fever, malaise, and leukocytosis known as "Metal Fume Fever" (MFF). The purpose of this study is to delineate the mechanism of this syndrome. Study hypotheses are: (1) MFF is a systemic response to ZnO_2 fume inhalation that results from the synthesis and release of cytokines acting as chemotactic factors and as endogenous pyrogens. One manifestation of the ZnO_2 mediated release of cytokines is a local inflammatory response in the lung. (2) The pulmonary macrophage, which may act in concert with other cells resident in the lung, is pivotal in response to ZnO_2 fume inhalation. Elucidating the mechanism of ZnO_2's effect will

address a group of illnesses representing an important clinical problem in occupational medicine. Furthermore, ZnO_2 inhalation provides a useful model in which to study general mechanisms of cellular responses to inhaled toxins in the human lung together with their pulmonary function and systemic manifestations. Better understanding of these mechanisms may also provide the basis for therapeutic interventions aimed at preventing or ameliorating the effects of inhaled toxins.

Specific study aims are: (1) To investigate whether inhalation of ZnO_2 fume is associated with a dose-dependent inflammatory response in the lung by measuring total and differential cell counts in the bronchoalveolar lavage (BAL). (2) To investigate possible functional changes associated with MFF pulmonary inflammation by assessing lung flows, volumes, diffusing capacity for carbon monoxide (DLco), airway resistance, and airway responsiveness. (3) To investigate whether there is a ZnO_2 fume dose-dependent presence of cytokines in the bronchoalveolar lavage (BAL) associated with the inflammatory pulmonary response and the systemic symptoms of MFF. (4) To investigate if there is a ZnO_2 dose-dependent synthesis and release of cytokines *in vitro* by purified human pulmonary macrophages in cell culture. These studies are intended to examine the hypothesis that ZnO_2 inhalation, pulmonary macrophage activation, cytokine-mediated inflammation, and the pulmonary and systemic manifestations of MFF are linked.

Methodology

We study subjects who perform electric welding on galvanized materials. Exposures are carried out within a specially designed environmental chamber. This chamber allows controlled ventilation and air turnover. The goal of these exposures is to simulate real-world conditions routinely encountered by most welders when they weld galvanized material. Personal breathing zone air sampling data provides an assessment of the level of exposure experienced. Because we wish to better understand the mechanisms of ZnO_2's pulmonary effects, we measure pulmonary function and airway responsiveness to methacholine at baseline and again 1 hour and either 6 or 20 hours following exposure. In order to study ZnO_2 effects on the cellular level, we also carry out bronchoscopy with bronchoalveolar lavage (BAL) at either 8 or 22 hours post-exposure, analyzing cell numbers and types, and measuring by immunodetection the cytokines IL-1 and TNF. We also monitor body temperature and the peripheral cellular response and serum zinc levels so that we may correlate these with the pulmonary effects we observe.

Significant Findings

Although the project is in its early phases, we have carried out exposures to ZnO_2 welding fume in 11 pilot study subjects. These pilot data demonstrate a dose-dependent pulmonary inflammatory response to ZnO_2 inhalation involving increases in PMNs, macrophages, and certain lymphocyte sub-types. The effect of ZnO_2 fume inhalation on these outcome measures is dramatic with a very high correlation between exposure and effect. This relationship provides powerful experimental evidence of a pulmonary inflammatory response. The inflammatory changes observed did not correspond to a marked functional change in pulmonary function as assessed by airflow, resistance, airway reactivity, or DLco. This apparent divergence between inflammation assessed by BAL and pulmonary function testing is intriguing and remains to be explored more fully with more data points over a wider range of exposures, including additional subjects followed at 6-8 hours post-exposure. There is an indication that the BAL response differs significantly at 8 as compared to 22 hours post-exposure. Despite the apparent linearity of the inflammatory dose-response, clinically manifest MFF exhibited a possible "threshold." This is consistent with the hypothesis that MFF may be mediated by cytokines, one effect of which is the degree and cellular characteristics of the pulmonary inflammatory response associated with ZnO_2 inhalation. Further analysis, including the proposed cytokine analysis and *in vitro* study components, will provide important additional experimental data.

Asbestos-Induced Pleural Fibrosis and Lung Restriction

David A. Schwartz, M.D., M.P.H.
University of Iowa
The Pulmonary Disease Division
Department of Internal Medicine
Room C33, GH
Iowa City, Iowa 52242

Program Area: *Occupational Lung Diseases*
Grant Number: *1 K01 OH00093-01*
Start & End Dates: *07/01/90 - 06/30/93*
Funding Level: *$40,838 ($40,838 Cum)*

Importance to Occupational Safety and Health

The overall goals of this project are to improve and advance the current criteria established by the International Labor Organization (ILO) to evaluate chest wall abnormalities and to understand-the determinants of restrictive lung function in asbestos-induced pleural fibrosis. Together, circumscribed pleural plaques and diffuse pleural thickening, are the most frequent radiographic abnormality among asbestos-exposed workers. The radiographic criteria established by the ILO to define and classify circumscribed pleural plaques and diffuse pleural thickening have not been adequately evaluated. Moreover, the association between pleural fibrosis and restrictive lung function was not considered when establishing these radiographic criteria. Although several groups have established a relationship between restrictive lung function and both circumscribed pleural plaques and diffuse pleural thickening the determinants accounting for this association have not been adequately addressed. Our preliminary studies indicate that restrictive lung function among those with asbestos-induced pleural fibrosis is, in part, caused by subradiographic inflammation and fibrosis of the lung parenchyma. These findings lead us to hypothesize that more sensitive indicators of parenchymal injury will allow us to fully understand the determinants of restrictive lung function in persons with asbestos-induced pleural fibrosis. The hypotheses put forth in this proposal are designed to investigate the accuracy of the diagnostic criteria established by the ILO, evaluate the anatomic and functional validity of these criteria, and identify the determinants of restrictive lung function among individuals with asbestos-induced pleural plaques and diffuse pleural thickening.

Objectives

1. Evaluate the anatomic and functional validity of the criteria established by the ILO identify and classify pleural fibrosis and, using these findings, develop an improved classification system for pleural abnormalities.
2. Use sensitive physiologic, radiographic, and biologic measures to control for the presence of parenchymal fibrosis while investigating the relationship between asbestos-induced pleural fibrosis and restrictive lung function.

Methodology

We will use a nested case-control study design with 120 subjects randomly selected from a large cohort (N-1,211) of sheet metal workers who have recently undergone a screening medical evaluation. Using chest x-rays, chest CT scans, and physiologic measures of lung function, we will evaluate the reliability and validity (anatomic and functional) of the current ILO criteria for pleural fibrosis. We will also use sensitive physiologic (progressive exercise ergometry and lung and chest wall compliance), radiographic (high resolution CT scans), and biologic (bronchoalveolar lavage cellularity) measures to control for the presence of parenchymal fibrosis while investigating the relationship between asbestos-induced pleural fibrosis and restrictive lung function.

Significant Findings

To further define the relationship between asbestos-induced pleural fibrosis and restrictive lung function, we investigated the pleural determinants of respiratory symptoms and restrictive physiology in 1,211 sheet metal workers. We specifically evaluated the relationship between components of pleural fibrosis (costophrenic angle involvement, diaphragmatic plaques, width and length of pleural fibrosis, pleural calcifications, and type of pleural fibrosis - circumscribed pleural plaque or diffuse pleural thickening) and both forced vital capacity (FVC) and respiratory symptoms. After controlling for the appropriate confounding variables, we found that costophrenic angle involvement ($p=.004$), the width ($p=.037$) and length ($p=.0001$) of pleural fibrosis, and the presence of either circumscribed plaques ($p=.0006$) or diffuse pleural thickening ($p=.0003$) were each significantly associated with a lower FVC. No significant relationship was observed between FVC and either diaphragmatic plaques or pleural calcifications. However, since the pleural abnormalities are highly colinear, none of these abnormalities alone or in combination predicted the decline in FVC better than circumscribed plaques or diffuse pleural thickening. Next, we investigated the relationship of each component of pleural fibrosis with three respiratory symptoms: cough, dyspnea, and chest pain. After controlling for appropriate confounders, a marginally significant relationship was observed between increased width and length of pleural fibrosis and dypsnea. Otherwise, these pleural abnormalities were not consistently related to any of the three respiratory symptoms. Our results indicate that although pleural plaques and diffuse pleural thickening and their components are independently associated with a lower FVC, these components of pleural fibrosis do not substantially improve the previously defined relationship between FVC and either circumscribed pleural plaques or diffuse pleural thickening.

Thus far, we have performed exercise ergometry on approximately twenty patients with asbestos-induced lung disease. In addition, we have worked out the methodology to perform lung compliance measures on these study subjects and will soon perform this measurement as part of our testing protocol.

Publications

Schwartz DA, Fuortes LJ, Galvin JR, Schmidt LE, Leistikow BN, LaMart FP, Merchant JA: Asbestos-induced Pleural Fibrosis and Impaired Lung Function. Am Rev Respir Dis 141:321-326, 1990

Schwartz DA, Galvin JR, Dayton CS, Stanford W, Merchant JA, Hunninghake GW: Determinants of Restrictive Lung Function in Asbestos-induced Pleural Fibrosis. J Appl Physiol 68:1932-1937, 1990

Schwartz DA: New Developments in Asbestos-induced Pleural Disease. Chest, in press, 1990

Schwartz DA, Redlich CA: Biomarkers of Occupational Lung Disease. Seminar Resp Med, in press, 1990

Immune Responsiveness in Chlorine Exposed Rats

Carol E. O'Neil, Ph.D.
Tulane University School of Medicine
1700 Perdido Street
New Orleans, Louisiana 70112

Program Area: *Occupational Lung Diseases*
Grant Number: *5 R03 OH02425-02*
Start & End Dates: *09/29/87 - 09/28/90*
Funding Level: *$22,500 ($45,000 Cum)*

Importance to Occupational Safety and Health

Long-term effects on respiratory health of acute high level exposures to non-sensitizing irritant gases are not fully understood. Irritant exposures may induce or exacerbate airway obstruction in some individuals or may increase susceptibility to inhaled antigens. Industrial gases, like chlorine, may also increase sensitivity to environmental antigens; however, they have not been well studied. Chlorine is an industrial chemical used in over 50 occupations, including pulp and paper processing and water sanitation. Over 15,000 individuals have potential exposure to this agent. High level, acute exposures may occur during an industrial accident; and it is important to determine the effects on respiratory health of this type of exposure. If our findings indicate substantial risk of enhanced susceptibility to antigen sensitization, this would provide guidance in the design of studies or surveillance programs for exposed working populations. Inclusion of appropriate tests for clinical follow-up of exposed individuals would also be warranted.

Objectives

The objective of this grant is to use a mouse model to determine whether acute chlorine exposure enhances sensitization to aerosolized antigen.

Methodology

Mice are exposed for 1 hour to chlorine gas (200 parts per million [ppm] or 150 ppm) or to breathing air. Briefly, whole body exposures take place in a stainless steel and glass horizontal laminar flow exposure chamber. Animals are observed at all times during the exposure period. As a safety precaution for laboratory personnel, the chlorine gas generation system is turned off after the termination of exposures. Air flow in the chamber is maintained until a continuous monitor indicates that the gas concentration in the chamber is one-half of the OSHA permissible exposure limit. A self-contained breathing apparatus is immediately available for all personnel.

Immediately, 3 hours, or 1, 7, 30, or 60 days post-chlorine exposure, mice are exposed, by nose only, to 1% bovine serum albumin (BSA). Antigen exposures are performed for 30 minutes for 5 consecutive days. Animals are then rested for 10 days. Test sera and bronchoalveolar lavage fluid (BALF) are obtained at sacrifice. Sera are obtained by retroorbital bleeding and BALF is obtained by *in situ* lavage of both lungs. For quantitation of antibodies, BALF is concentrated approximately 15 times by Amicon ultrafiltration. Antigen (BSA) specific IgG, IgA, and IgM antibodies are quantitated in sera and BALF using an enzyme linked immunosorbent assay (ELISA). This is a standard assay, except that goat sera has been substituted for BSA in all appropriate solutions. Data from test animals are compared with those obtained from non-chlorine exposed controls.

Significant Findings

Animals exposed to the highest concentration of chlorine (200 ppm) and immediately to antigen had the highest levels of BSA-specific IgG antibodies. However, mice exposed to antigen more than 3 hours after chlorine exposure did not demonstrate increased antibody levels. Mice exposed to 150 ppm chlorine and subsequently exposed to BSA did not demonstrate increased production of class specific antibodies. Results suggest that exposure to near toxic levels of chlorine are associated with enhanced sensitization to antigen; however, recovery is rapid. Animals exposed to breathing air (controls) did not demonstrate production of class specific antigens.

Exposure Estimation and PFT's for U.S. Coal Miners

Thomas G. Robins, M.D.
University of Michigan
School of Public Health
Occupational Health Program
Ann Arbor, Michigan 48109-2029

Program Area: *Occupational Lung Diseases*
Grant Number: *1 R03 OH02627-01*
Start & End Dates: *09/30/88 - 09/29/90*
Funding Level: *$21,349 ($21,349 Cum)*

Importance to Occupational Safety and Health

In order to control the incidence of coal workers' pneumoconiosis (CWP), exposure to respirable coal mine dust has been strictly controlled in the United States since 1970 by the Coal Mine Health and Safety Act (CMHSA) of 1969. Exposure to coal mine dust is also associated with the development of chronic obstructive pulmonary diseases (COPD) including emphysema and chronic bronchitis. To accurately study the relationship between exposure to coal dust and the associated respiratory conditions since the CMHSA was enacted, accurate estimates of exposure are required. This study will quantitate exposure to respirable coal mine dust in a sample of U.S. coal mines from 1970 to the present. The estimated exposures will then form the basis for exposure-response analyses for CWP and COPD outcomes in a cohort of miners under study by the NIOSH. These analyses will then provide valuable information for evaluating the effectiveness of the CMHSA in preventing occupational lung disease in U.S. coal miners.

Objectives

1. To quantitatively estimate the exposure levels of respirable coal mine dust for a cohort of underground miners.
2. To assess the relationships of coal mine dust exposures to various respiratory outcomes using both cross-sectional and longitudinal designs.

Methodology

Accurate and precise estimates of exposure for the cohort were developed using compliance data collected by the Mine Safety and Health Administration (MSHA). Arithmetic mean concentrations were estimated within work categories defined by mine, occupation, and year and decreasingly-specific categories, occupation/year, mine/year, and year.

Exposure-response relationships were examined among 1,270 miners from the National Study of Coal Workers' Pneumoconiosis. Cross-sectional and longitudinal associations between cumulative exposure and pulmonary function test results (FVC, FEV_1, and FEV_1/FVC) and respiratory symptoms were modeled using linear and logistic regression while controlling for smoking.

Significant Findings

1. Accurate and precise estimates of exposure for epidemiologic research may be constructed using Mine Safety and Health Administration (MSHA) air sampling data for underground coal mines.
2. Several biases have been identified in the MSHA data and some of them have been quantified. Of most importance is the finding that operator-collected data has a disproportionate number of samples at 0.1 mg/m^3 resulting in an estimated -13% bias in the mean concentrations.
3. Cross-sectional results over a 15-year exposure period indicated statistically significant positive associations of cumulative exposure with decrements in FEV_1, FEV_1/FVC; the likelihood of these indices being less than 80% of predicted; and symptoms, including chronic bronchitis, breathlessness, and wheeze, with shortness of breath. The estimated effect of exposure on FEV_1 was 5.5 ml per mg/m^3-years which was substantially larger than previously reported estimates.

4. Cross-sectional results within five years of the beginning of exposure demonstrated a rapid initial exposure-related loss of both FVC and FEV_1 on the order of 25 ml per mg/m^3-years.
5. Using a longitudinal approach, no exposure-related change in pulmonary function was detected over the approximately 13-year period studied, although pulmonary function as a percent of predicted did decline.

Publications

Seixas NS, Robins TG, Rice CH, Moulton LH: Assessment of Potential Biases in the Application of MSHA Respirable Mine Dust Data to an Epidemiologic Study. Am Ind Hyg Assoc J 51:534-540, 1990

Seixas NS, Robins TG, Moulton LH: The Use of Arithmetic Versus Geometric Means in Exposure Assessment. Am J Ind Med 14:465-477, 1988

Seixas NS, Robins TG, Attfield MD, Moulton LH, Rice C, Weeks JL: Exposure Estimates for the National Coal Study: The Use of MSHA Compliance Data for Epidemiologic Research. Presented at the VIIth International Conference on the Pneumoconioses, Pittsburgh, PA, August, 1988. Proc of the VIIth International Conference on the Pneumoconioses, in press, 1988

Immuno-Epidemiology of Crab-Induced Occupational Asthma

Carl M. Shy, M.D., Dr.P.H.
University of North Carolina
CB#7400 School of Public Health
Department of Epidemiology
Chapel Hill, North Carolina 27599-7400

Program Area: *Occupational Lung Diseases*
Grant Number: *5 R03 OH02654-02*
Start & End Dates: *04/01/89 - 03/31/91*
Funding Level: *$21,675 ($43,350 Cum)*

Importance to Occupational Safety and Health

This research should be useful in determining the prevalence of various general health conditions among women (predominantly black) employed in the crab processing industry. Specifically, the population of interest is crab-pickers, women who break open cooked crabs and extract or "pick" the edible meat. All of these employees are exposed to blue crab (Callinectes sapidus) tissues and fluids (potential allergens) and engage in highly repetitive motions. Therefore, the major focus of the study will be on allergy-related disease, ranging from allergic contact dermatitis to asthma, and a secondary emphasis will be on musculoskeletal problems, particularly relating to the hands. By comparing these conditions with the same among a sample of former crab pickers, the extent to which occupational diseases lead to outward migration from the workforce may be examined. If the prevalences of allergic and/or musculoskeletal diseases are higher among former workers compared with current workers, the potential for preventive interventions would be a reduction in occupational morbidity, reducing or eliminating the need to terminate employment for health reasons. This is especially valuable in areas with high unemployment.

Objectives

The central research question to be addressed in this study is whether or not women occupationally exposed to blue crab develop occupational allergies and if so, whether they selectively migrate out of the workforce. The specific study goals which directly address the research question include the following:

1. To estimate the prevalence of occupational allergic diseases, including asthma, bronchitis, hay fever, and dermatitis, as well as prevalence of hypersensitivity (IgE response) to crab antigen among women actively employed as crab pickers in North Carolina;
2. To document an outward worker migration possibly related to hypersensitivity to crab or to respiratory symptoms;
3. To describe any differences between current and former workers in terms of demographic characteristics, health history, and hypersensitivity as determined by skin testing; and
4. To assess the possible role of musculoskeletal problems, especially of the hands, in influencing employment patterns among crab pickers.

Methodology

Based on an enumeration of all crab pickers employed for at least one day between January 1, 1986 and December 31, 1989, samples of active employees and former employees were invited to participate in this study. All participants were

interviewed to determine relevant health history, and skin tested for allergies, including negative and positive controls, for common environmental allergens, as well as three different crab preparations. Skin tests were applied to the inside surfaces of both forearms prior to interview, and the test results recorded 20 minutes later. Data analysis will determine prevalences of self-reported health outcomes among current workers, which will be compared with those among former workers, to determine the role of adverse health events in leaving the industry prior to retirement.

Significant Findings

The study is currently in the final stages of analysis. Analyses have been completed for objectives one through three above, and are underway for the fourth.

Data on 257 participants were included in the final analysis files, consisting of 204 currently employed crab pickers and 53 former employees. Currently employed crab pickers were found to be significantly older, and as could be expected, had significantly longer duration of employment than former employees. However, with respect to height, weight, education, race, and tobacco use (cigarettes and smokeless tobacco), the two groups were virtually identical. Following is a list of the important study findings:

1. Former crab pickers were more likely than current crab pickers to have reported an occupational health problem (OR = 3.4, CI = 1.5, 7.4), changing jobs for a health reason (OR = 3.0, CI = 1.1, 8.2), and having quit a job because of a problem with the hands (OR = 5.5, CI = 2.6, 11.3), but the two groups were similar with respect to missing work for a health reason (OR = 0.9, CI = 0.5, 1.8);
2. Former crab pickers were more likely than current crab pickers to have reported a variety of symptoms, including runny nose, sore throat, sinus problems, fever and chills, headache, cough, and shortness of breath (OR's range from 1.9 to 4.8) but not eye problems, phlegm or hand dermatitis (the latter two were associated with being a current employee);
3. Former crab pickers were more likely than current crab pickers to have reported allergic symptoms related to pollen and dust (but not to smoke and detergent, which are not allergens);
4. Based on skin test results using a commercially prepared antigen, 9.5% of current and 22.0% of former crab pickers produced a positive skin test, but the other two crab solutions produced nearly equivocal results (16.4% vs. 18.0% and 7.0% vs. 10.0%, respectively);
5. The strongest skin test result correlating with employment status was the response to the negative control solution, suggesting that as a group, former employees were more generally reactive to non-specific stimuli; and
6. Among skin test responses, reactions to uncooked crab and dust mite preparations were correlated, suggesting a possible cross-reactivity.

Final results on the musculoskeletal data will be available within the next few months. Preliminary screening suggests that upper extremity and low-back complaints are most common, with prevalences exceeding 30%.

Publications

Mundt KA: Occupational Asthma and the "Healthy Worker Effect" Among Women Employed in the Seafood Processing Industry. American Journal of Epidemiology 132:761, 1990

Development of a Model for Prediction of Optimal Lifting Motion

Mohamed M. Ayoub, Ph.D.
Texas Tech University
Department of Industrial Engineering
P.O. Box 4130
Lubbock, Texas 79401-4130

Program Area: *Musculoskeletal Injuries*
Grant Number: *5 R01 OH02434-03*
Start & End Dates: *01/01/88 – 12/31/90*
Funding Level: *$41,963 ($200,928 Cum)*

Importance to Occupational Safety and Health

The cause of health hazards that occur in manual material handling (MMH) tasks is overexertion (load stress). A reasonable approach towards solving problems is to redesign the task or the workstation to better fit the human body. This research intends to develop software to simulate and animate the motion patterns of selected joints in a MMH task. The prediction of the motion patterns would be reliable enough to represent most probable movements of a given human body for a specific task and workstation under design. Based on the output of the simulation, the workstation designer can evaluate design characteristics and make changes to the manual material handling task and the modeling geometry as needed.

Objectives

The intent of this study is to simulate the angular movement of five human joints based on the invariant characteristics of manual lifting that are multidirectional and multiarticular and executed by large muscle groups generating torques within maximum capacity. With few exceptions, simulation of human body motion is a multidisciplinary activity. It requires combining information from the biomechanical and psychophysical approaches of ergonomics with knowledge of behavioral sciences. This study does not attempt to apply all the varied knowledge in the general field of human factors. Rather, it deals with only one set of performance limitations of manual lifting, those produced by the understanding of human physical capacities and task requirements. Therefore, this study characterizes the angular displacement of each joint associated with such a performance, including the extent of the movement simulated.

Methodology

The magnitude of the force of each joint is predicted for each time increment of the lifting motion. Model constraints are based on the limitations imposed by the task, the work place, and the characteristics of the body. Two major tools were developed during FY90:

1. Development of Algorithms

New algorithms were developed to construct a feasible path and work towards optimality with each iteration. The first method (simulation technique) proceeds as follows:

a. A Set Generator Function (SGF) is selected. This, in turn, generates a set of motion paths for the five joints of the body.
b. If there is more than one feasible path, the path with the "best" objective function value is selected.

In the above technique, the global optimum is not guaranteed. To remedy this problem, a second method (gradient technique) was developed:

a. A Generalized Reduced Gradient algorithm is utilized with the desired objective function and a set of physical, kinematic, and kinetic constraints.
b. The algorithm goes on improving the initial solution until the change in objective function value is less than a specified criteria.

2. An animation package was developed.

In order to better understand the human lifting pattern, and to compare the model and the subject, an animation package coded in C was designed.

Significant Findings

Effort has been mainly focused on determining the right objective function that the body minimizes during the movement. It was observed after studying the effect of 8 objective functions that no single objective function seems to be perfectly satisfactory. It was also observed that the body during the course of lift does not necessarily minimize an objective function, but instead, after reaching a certain point, the body seems to be unable to differentiate between the small differences in the objective function values. Efforts are still directed to fine tune the model to achieve solutions closer to those observed.

Publications

Ayoub MM, Blair EL: From Biomechanical Modelling to Biomechanical Simulation. Proc of Human-Centered Design Technology for Maintainability Workshop. Air Force Human Resources Laboratory, Wright-Patterson Air Force Base, Ohio, September 13, 1990

Lee YH: Toward Electronic Work Design. Proc of Human Factors Society, 32nd Annual Meeting, Volume 1, pp 622-626, 1988

Back Injuries in Municipal Employees

Ann H. Myers, Sc.D.
The Johns Hopkins University
School of Hygiene and Public Health
624 N. Broadway
Baltimore, Maryland 21205

Program Area: *Musculoskeletal Injuries*
Grant Number: *5 R01 OH02574-03*
Start & End Dates: *09/30/88 - 09/29/91*
Funding Level: *$213,159 ($595,556 Cum)*

Importance to Occupational Safety and Health

Low back injuries account for more absence from work than any other disease. Municipal employees are a high risk group. In order to design interventions to reduce injuries, it is necessary to identify the risk factors associated with the injuries. A multi-disciplinary team of researchers is working with the Baltimore City Office of Occupational Medicine and Safety, the Deputy Labor Commissioner, labor union representatives, and Departmental staff in a casecontrol study of employees in the four departments in the City of Baltimore with the highest rates of low back injury: Public Works, Education, Transportation, and Recreation and Parks.

Objectives

1. Describe the nature, type, and circumstances of back injury;
2. Determine if work characteristics, work patterns, hazardous exposures, material handling practices, and personal and job stressors differ between cases and matched controls;
3. Develop specific recommendations to reduce occupational low back injury based on the above findings; and
4. Evaluate a new method of collecting data (by interview) for an ergonomic analysis of job task among those reporting lifting, lowering, pulling, pushing and pressing.

Methodology

Data collection for the study began March 1, 1990. Cases are identified by the study coordinator in the Occupational Medicine Clinic through the collection of injury reports, clinic slips, and medical records. The study has collected 153 (116 males and 37 females) of its necessary 200 cases, and at the current rate, data collection is on schedule. The controls are identified through the four departmental personnel offices, and the names and telephone numbers of persons with similar job titles, work locations, and sex are relayed to the study coordinator.

Information about the cases/controls is provided to Survey Research Associates (SRA) to conduct interviews. A sample of site visits is being arranged with selected cases to reconstruct their activity at the time of the injury. Permission is obtained prior to the site visits. The average interview time is 72 minutes, averaging less for controls and more for cases. The completed and edited interviews, once returned from SRA, are readied for key punching. It was decided that the raw ergonomics sections of the questionnaire would be sent to the consulting ergonomist for his staff to clean, code, and perform the data entry. He will do the ergonomic analysis of selected tasks, using appropriate analytic techniques. To date he has received 49 complete sets of cases and their matched controls. We are beginning preliminary analyses. Ergonomic data from the questionnaire will be compared with the site visit data.

Significant Findings

None to date.

Ergonomic Injury Control in High Frequency Lifting Tasks

Shihab Asfour, Ph.D.
University of Miami
Industrial Engineering Department
P.O. Box 248294
Coral Gables, Florida 33124-0623

Program Area: *Musculoskeletal Injuries*
Grant Number: *3 R01 OH02591-02S1*
Start & End Dates: *09/30/88 - 11/29/90*
Funding Level: *$113,781 ($205,856 Cum)*

Importance to Occupational Safety and Health

This study is unique in that industrial workers, rather than student volunteers, were used in a controlled laboratory setting to establish a knowledge base of workers' physiological endurance limits for high frequency manual lifting tasks. The results from this study should help health and safety professionals better understand the relationship between endurance time, load, and musculoskeletal injury and improve work performance.

Objectives

The main objective of this research is to develop a knowledge base of workers' physiological endurance limits for high frequency lifting tasks. Worker lifting endurance will be determined through a set of predictive models that will be developed in the principal investigator's laboratory at the University of Miami, using a large sample of male industrial workers. A knowledge-based system will be developed using the information collected from the laboratory study. This system can be used by companies in the design or redesign of continuous high frequency lifting tasks.

Methodology

The methodology used in this research was a modified psychophysical approach where the subject was given control of lifting duration rather than the amount of load lifted. Human lifting capabilities were determined by designing and conducting an experiment in the principal investigator's laboratory covering a wide range of loads (5, 10, 15 kg) and high frequencies (8,12,16 lifts/minute) for two different age groups. The three heights of lifts studied were floor to table, table to shoulder, and shoulder to reach. The two age groups for the subjects were those between 20 years and 30 years, and those between 31 years and 40 years of age. To date, a total of 54 subjects have been tested. The duration of each experimental session, referred to as endurance time, was treated as a response variable.

A metabolic monitoring system (MMS) was used to measure the oxygen consumption and minute ventilation of the subject while performing the lifting task. Three surface electrodes, affixed to the subject's chest and connected to a cardiac monitoring system (CMS), were used to record the heart rate of the subject while performing the task. The oxygen consumption, minute ventilation, and heart rate were measured continuously on a minute-to-minute basis. Due to the exorbitant volume of data collected, analysis was conducted at 5-minute data intervals.

Endurance time in this study was defined as the maximum length of time during which an individual is capable of continuously lifting a given load at a given frequency for a specific height. The upper limit for endurance time was set at 8 hours. Each subject was given 10 minutes of rest for every 50 minutes of work and 1 hour for lunch after the four hours of work. The ratings of perceived exertion (leg, back, arm, shoulder, hand, overall body, and local) was recorded after every 50 minutes of work and upon termination of the experimental session. The task consisted of lifting a compact box (38 x 38 x 25 cm) using a freestyle lifting technique in an environmentally controlled laboratory. A mechanical device automatically lowers the box after each lift.

Significant Findings

The studies conducted concentrated on data collection of endurance time and physiological responses of subjects for the different treatments. To date, a total of 486 treatments have been completed. This included 9 subjects in each age group for each height level. Each subject had to undergo 9 treatments of different load frequency combinations.

The data collected was analyzed using the ANOVA procedure in SAS. For floor to table height, age was found to have a significant effect on endurance time and heart rate while it did not affect minute ventilation and oxygen consumption significantly. Load and frequency of lift were found to have a significant effect on endurance time, heart rate, minute ventilation, and oxygen consumption. For table to shoulder height and shoulder to reach height, age had no significant effect on endurance time, heart rate, minute ventilation, or oxygen consumption. However, the load lifted had

significant effects on all the above variables for both table to shoulder and shoulder to reach heights. Lifting frequency had a significant effect on endurance time, heart rate, minute ventilation, and oxygen consumption for table to shoulder height, while for shoulder to reach height, it affected only endurance time and heart rate significantly.

For floor to table height and age group 1 (20 years to 30 years), the mean endurance time was 473.3 minutes for the lowest load frequency combination (11 lbs/8 times per minute) and 172.1 minutes for the highest load frequency combination (33 lbs/16 times per minute). For age group 2 (31 years to 40 years), the above values were 415 minutes and 125.1 minutes respectively.

For table to shoulder height and age group 1 (20 years to 30 years), the mean endurance time was 439.8 minutes for the lowest load frequency combination (11 lbs/8 times per minute) and 204.6 minutes for the highest load frequency combination (33 lbs/16 times per minute). For age group 2 (31 years to 40 years), the above values were 459.4 minutes and 166.9 minutes respectively.

For shoulder to reach height and age group 1 (20 years to 30 years), the mean endurance time was 446.2 minutes for the lowest load frequency combination (11 lbs/8 times per minute) and 77.6 minutes for the highest load frequency combination (33 lbs/16 times per minute). For age group 2 (31 years to 40 years), the above values were 458.8 minutes and 56.9 minutes, respectively.

Publications

Jomoah IM, Asfour SS, Genaidy AM: Physiological Models and Guidelines for Design of High Frequency Arm Lifting Tasks. Advances in Industrial Ergonomics and Safety II, (eds. W Karwowski, J Yates), Taylor & Francis, London, 1991

Asfour SS, Genaidy AM, Fahmy MW, Younis A, Waly SM: Endurance and Physiological Responses for High Frequency Lifting Tasks: A Preliminary Report. Advances in Industrial Ergonomics and Safety II, (ed. B Das), Taylor & Francis, London, 1990

Quantitative Measures of Wrist Motions

William S. Marras, Ph.D.
The Ohio State University
Industrial and Systems Engineering
1971 Neil Avenue, Room 210
Columbus, Ohio 43210

Program Area: *Musculoskeletal Injuries*
Grant Number: *5 R01 OH02621-02*
Start & End Dates: *01/01/89 – 12/31/90*
Funding Level: *$35,968 ($69,216 Cum)*

Importance to Occupational Safety and Health

Cumulative trauma disorders (CTDs), also known as repetitive trauma disorders, are disorders of the soft tissues (most commonly the tendons, muscles, and nerves) due to repeated exertions and excessive movements of the body. Workers in industrial tasks who have to move their hands and wrists repeatedly and/or forcefully are susceptible to CTDs. Some specific CTDs of the hand and wrist are carpal tunnel syndrome (CTS), tenosynovitis, and De Quervain's disease.

The overall incidence of CTDs in industry is unknown, but epidemiological data reveal that CTDs are a rapidly growing problem. Overall, CTDs are the second most frequent category of occupational illness after skin disease. Recent statistics from the Department of Labor indicate that repetitive injuries now account for 48 percent of occupational illnesses. This has increased from 18 percent just seven years ago. Finally, OSHA has focussed upon these types of disorders and has labeled them "the diseases of the 90's".

Wrist posture and repetition have often been cited qualitatively as risk factors associated with CTD's. However, research has not identified the degree of wrist bend or amount of repetition that places the worker at risk. A quantitative assessment of the wrist positions and motion patterns is needed to truly understand and control the risk associated with CTDs. Quantitative measures could serve as a foundation of a work practices guide that could be used in industry to redesign repetitive jobs so that the risk of suffering a CTD is minimized.

Objectives

It is widely accepted that CTDs are related to the motions of the hand and wrist during work.

However, a void exists in the literature in that we do not understand which characteristics of a repetitive motion relate to increased risk of suffering a CTD. The objective of this research is to examine the correlation between kinematics of wrist motion and the risk of suffering a specific occupationally related CTD, carpal tunnel syndrome. Specifically, wrist position, velocity and acceleration in the flexion/extension, radial/ulnar, and pronation/supination hand planes of workers performing highly repetitive jobs in industry will be correlated with CTD risk. The results of this correlation analysis will be used to determine which specific wrist motion characteristics are associated with an increased incidence of CTS. The data collected in this research will be used to construct a preliminary set of work practice guidelines on how to reduce the incidence of CTS in repetitive assembly work.

Methodology

This research was implemented in three stages.

1. Development of Quantitative Methods. A wrist monitor developed in the Biodynamics Laboratory at The Ohio State University was used to record the positions, velocities, and accelerations of the wrists in all possible planes of motion. This monitor has been found to be quite accurate, is easy to fit to subjects, and does not require individual calibration.
2. Industrial Documentation of Wrist Motions. The wrist monitors were placed upon the hands of industrial workers who performed highly repetitive jobs. Jobs were selected for documentation where the risk of a CTS was either high or low. High risk jobs were identified where the risk of injury was at least 8 incidences per 200,000 hours of exposure. Low risk jobs were defined as those where the risk of injury was less than 3 incidences per 200,000 hours of exposure. The incidence was determined via the OSHA 200 log data and medical records. Forty subjects were examined in this study (20 high risk and 20 low risk).
3. Analysis and Interpretation. The wrist motion kinematic variables were evaluated for the significance of difference between the groups as well as for the level of correlation within the CTD risk group.

Significant Findings

This study has shown that there was no statistically significant relationship (in any plane of the wrist or forearm) between the mean wrist position, maximum wrist position, or minimal wrist position observed while working in a repetitive job and the risk of suffering a CTS injury. However, in each wrist or forearm plane, range of wrist motion, mean wrist angular velocity, maximum angular wrist velocity, minimum angular wrist velocity, mean angular wrist acceleration, maximum angular wrist acceleration, and minimum angular wrist acceleration, were all positively and significantly associated with an increased risk of suffering a CTS. Furthermore, the greater the derivative of position, the more apparent the difference between the high and low risk group motion characteristics. In other words, acceleration was a better indication of risk than was range of motion. These findings are helping us to understand the manner in which motion increases the loading on biomechanical structures.

Publications

Schoenmarklin RW, Marras WS: A Dynamic Biomechanical Model of the Wrist Joint. Proc of the Human Factors Society 34th Annual Meeting, Orlando FL, October 8-12, pp 805-809, 1990

Schoenmarklin RW, Marras WS: An Investigation into the Effects of Angled Hammers and Hammering Orientation. Part I: Wrist Motion and Hammering Performance. Human Factors 31(4):397-411, 1989

Schoenmarklin RW, Marras WS: An Investigation into the Effects of Angled Hammers and Hammering Orientation. Part II: Muscle Fatigue and Subjective Impressions. Human Factors 31(4):413-420, 1989

Unexpected Trunk Loading Following Seated Vibration

David G. Wilder, Ph.D.
The University of Vermont
Department of Orthopaedics and Rehabilitation
Given Building #4
Burlington, Vermont 05405

Program Area: *Musculoskeletal Injuries*
Grant Number: *1 K01 OH00090-01*
Start & End Dates: *07/01/90 - 06/30/93*
Funding Level: *$54,000 ($54,000 Cum)*

Importance to Occupational Safety and Health

This work will study *in vivo*, the effects of common loading environments on the mechanical response of the seated human. The eventual goal of this work is to evaluate and control the occupational health hazard of low back pain, a musculoskeletal injury, by establishing an "envelope" of loading conditions which should not be exceeded if the spine is not to experience minimal mechanical damage. Proceeding from prior *in vitro* findings of short-column buckling in the lumbar spine following vibration exposure, this proposal will evaluate how the supporting trunk musculature responds to an unexpected load application after a one-hour load intervention (seated vertical vibration, seated lateral vibration, seated combined vibration, sitting still or lying supine). This will simulate the sudden and unexpected shift of an object in the hands of the car or truck driver who has driven for one hour. Normal walking (as a break) for ten minutes, prior to an unexpected load application, will also be tested to determine if it would be a reasonable control. This would allow lumbar discs to return, via creep behavior, to the upright posture orientation where the facets are more firmly engaged.

Objectives

The following hypotheses will be tested using a repeated measures analysis of variance technique:

1. There are significant differences in trunk muscle activity during unexpected load application between:
   (a) subjects with "lumbar instability" and normal controls and
   (b) subjects with different load exposure histories (seated vibration, sitting still, or lying supine).
2. There are significant differences in main and coupled mechanical driving point impedance characteristics during brief vibration exposures for mechanical response evaluation between:
   (a) subjects with "lumbar instability" and normal controls and
   (b) subjects with different load exposure histories (seated vibration, sitting still, or lying supine).
3. A walking break for 10 minutes "resets" the system.

By using these hypotheses, it will be possible to differentiate the effects of static and vibration loading and sitting and reclining postures on the trunk's neuromuscular control system. The overall goal is to establish the mechanical effect of load history on the lower back and to determine whether load history increases the likelihood of significant mechanical derangement following a sudden mechanical overload. This will begin to establish whether the International Standards Organization vibration exposure criteria are reasonable limits for minimizing mechanical changes in the lumbar region.

Methodology

Trunk muscle activity (via surface electromyography) and main and coupled mechanical driving point impedance (via brief vertical vibration exposures for mechanical response assessment) of the subjects will be recorded and used as the outcome measures of the tests. Sixty subjects will be tested, 30 of whom are diagnosed with "lumbar instability" and 30 age and gender matched normal controls. Outcome measures will be obtained before and after sustained exposure to specific loading environments. Trunk muscle activity will also be monitored during a sudden, unexpected flexion load applied to the subject, performed before and after sustained exposure to the specific loading environments.

Significant Findings

None to date.

Quantitative Assessment of Carpal Tunnel Syndrome

Fredric E. Gerr, M.D.
Mount Sinai Medical Center
DEOM Box 1057
10 E. 102nd Street
New York, New York 10029

Program Area: *Musculoskeletal Injuries*
Grant Number: *1 K01 OH00098-01*
Start & End Dates: *09/28/90 – 09/27/93*
Funding Level: *$53,991 ($53,991 Cum)*

Importance to Occupational Safety and Health

Carpal tunnel syndrome is a common nerve entrapment disorder. It is universally accepted that it is the clinical concomitant of median nerve entrapment at the carpal canal. At this time,

increasing evidence indicates that occupational factors, especially force and repetition, are etiologically related to its development. Other factors, such as awkward postures and vibration, have also been considered possible occupational etiologies, although the evidence relating these factors to the disorder is not as clear as for force and repetition.

Although electrophysiologic evaluation with nerve conduction testing and electromyography is considered the gold standard for confirmation of the diagnosis of carpal tunnel syndrome, it is seldom performed in epidemiologic studies of the occupational etiologies of this disorder. Electrophysiologic evaluations are not well suited to use in field studies of large populations of workers because they are noxious to the subject, take considerable time to perform, require careful control of testing conditions, utilize expensive equipment, and require highly trained personnel to administer. Field studies of carpal tunnel syndrome have therefore relied on clinical methods alone (symptoms and/or physical signs) to diagnose the condition. Unfortunately, clinical signs and symptoms alone are not sufficiently specific or sensitive for use in occupational epidemiology. The development of a quantitative, objective and valid test for carpal tunnel syndrome that is nonaversive, easy to administer, rapid, and does not require sophisticated equipment would be of value in research into the occupational etiologies of carpal tunnel syndrome by allowing better measurement of the outcome than is currently possible with symptoms and physical examination alone.

The primary goal of this project is to determine the sensitivity and specificity of vibrotactile threshold testing for the detection of carpal tunnel syndrome. Vibrotactile threshold testing has been used successfully in studies of other occupationally induced disorders of the peripheral nerves, including the hand-arm vibration syndrome and organophosphate-induced peripheral neuropathy. If found sufficiently sensitive and specific in the current study, it could be used to improve the accuracy of diagnoses of carpal tunnel syndrome in other studies.

Objectives

1. To determine the specificity and sensitivity of vibrotactile threshold testing for the diagnosis of carpal tunnel syndrome using a combination of characteristic signs, symptoms, and electrophysiologic findings as the "gold standard" for the diagnosis.
2. To compare the change in symptoms reported in patients after treatment for carpal tunnel syndrome to changes in both vibrotactile threshold measurement and electrophysiologic parameters.
3. To determine the magnitude and variability in change of vibrotactile threshold parameters over time by measuring them serially in a group of asymptomatic subjects free of carpal tunnel syndrome.

Methodology

To determine the sensitivity and specificity of vibrotactile threshold testing for the diagnosis of carpal tunnel syndrome, disease positive and disease negative groups will be established using well-defined "gold-standard" methodologies. In this context, both symptoms, signs, and the results of electrophysiologic tests will be utilized to establish disease positive and disease negative groups. Specifically, three groups will be defined: Group 1 - those with clinical and electrophysiologic evidence of carpal tunnel syndrome; Group 2 - those with symptoms suggestive of carpal tunnel syndrome, but free of electrophysiologic evidence of the disease; and, Group 3 - those free of both symptoms and electrophysiologic evidence of disease. Test outcomes of 80, 90, and 95% specificity will be estimated from both Groups 2 and 3. Estimates from Group 3 will be considered best case estimates.

To determine the relationship between change in symptoms following treatment and change in vibrotactile threshold and electrophysiological measures, all Group 1 subjects, regardless of treatment, will be invited to undergo repeat testing 7 months following entry into the study. The change in subjective symptomatology will be compared to changes in vibration threshold and electrophysiological parameters.

To determine the change in the magnitude and variability of vibrotactile thresholds in disease-free subjects, Group 3 subjects will be asked to undergo symptom review and repeat vibrotactile threshold testing 7 months after the first evaluation.

Significant Findings

None to date.

Biomechanical Assessment of Work Tasks and Musculature

Donna L. Wheeler
University of Florida
Department of Orthopaedics
Box J-246 JHMHC
Gainesville, Florida 32610-0246

Program Area: *Musculoskeletal Injuries*
Grant Number: *1 R03 OH02684-01*
Start & End Dates: *09/28/89 - 09/27/91*
Funding Level: *$21,750 ($21,750 Cum)*

Importance to Occupational Safety and Health

Workers engaged in manual material handling tasks are predisposed to "overexertion type" low back injuries. The lumbar extensor muscle group is most often at risk of injury and is considered the weak link in the worker's biomechanical system. The need for a realistic biomechanical model incorporating three-dimensional motion, optimal spinal links, and muscle tensions coinciding with the worker's strength prompted this research. This work would allow each model to be individualized through the worker's kinematics and strength of the lumbar extensor and rotator musculature. This analysis would allow identification of weaknesses in the worker's "machinery" and prompt repair (strengthening or improved flexibility). In addition, this model would allow assessment of a worker's lifting capacity during a rehabilitation program or following injury expediting return to work with defined limitations.

Objectives

The objectives of the proposed project are defined below:

1. Optimize the spinal links (number of vertebrae per link and number of links per spinal column).
2. Kinematic and kinetic analysis of dynamic 3-D motion (identification of forces and moments at defined joints).
3. Identification of lumbar extensor strength and rotator strength for normal uninjured subjects through MedX testing.
4. Correlation of estimated tension in musculature via biomechanical model and subject's capacity as measured by MedX testing. Using this correlation, the subject's lifting capacity is predicted.

Methodology

Kinematics and Kinetics. A reflective marker set (triad) was created which attaches to the subject's back allowing the section of the spine spanning the marker to be tracked as a plane moving through space. In order to optimize marker placement on the spine, optimize the number of vertebrae to be included in one link, and determine the optimum number of spinal segments, a validation procedure was performed on a wooden model with three known link lengths. Movement of the markers was tracked by a video-based motion analysis system designed to track human motion. Link lengths were predicted based on marker kinematics. The estimated link lengths were then compared to actual link lengths of the model. Following validation, the markers were transferred to a human spine and analyzed while performing complex 3-D motion. Optimal spinal segments were then identified for motions involved in typical work tasks. Refinement of optimization software continues using a "reverse kinematic analysis." In addition, equations modeling the dynamics of the human body during 3-D work task analysis are underway. Through this analysis, predictions of the muscle forces as well as forces and moments at each joint are possible.

Muscle Testing and 2-D Kinematic Analysis. A pilot study involving 2-D analysis of planar lifting motion was analyzed using software developed at the University of Michigan and promoted by Motion Analysis Corporation. Subjects (n=5) completed an extensive MedX examination to evaluate maximum isometric lumbar extensor strength at seven angles of trunk flexion. These subjects then proceeded to lift a light box while body kinematics were collected by the Motion Analysis system. L5S1 joint torques, compression and shear forces, and erector spinae tension were then estimated from this model. Due to the linear relationship between load lifted and L5S1 torque, the load lifted was incrementally increased using the kinematic data collected during the light lift. The load was increased until the L5S1 torque matched that of the maximum isometric lumbar extensor tension at a corresponding angle of hip flexion as measured on the MedX machine. This load was then considered to be an estimate of the absolute maximum load a subject can safely lift based on his/her strength.

Significant Findings

Kinematics and Kinetics. Early attempts to identify spinal links using optimization techniques were problematic due to the sensitivity to inherent kinematic noise and an infinite number of correct solutions. Limiting variables to make the solution tractable led to the assumption of 3 rotations at each marker plus a slider at each link junction. This led to a new model for consideration - a "manipulator" model with three cylindrical joints allowing simulation of 6 degrees of freedom between each marker triad. Using a reverse analysis allows calculation of these joint angles and slider lengths and provides a closed form, unique solution for link parameters. Preliminary utilizations of this algorithm has shown it to be controllable and to yield appropriate quantitative results from the wooden validation model. Finalization of the program continues, as well as application to complex 3-D motions of the spine.

Muscle Testing and Kinematic Analysis. Preliminary data revealed a correlation between the maximum isometric erector spinae tension as measured by the MedX machine (reflective of L5S1 torque) to the L5S1 torque developed when lifting maximum loads as predicted using 2-D lift task modeling. Data collection continues to substantiate these findings.

A Longitudinal Study of Musculoskeletal Disorders

Laura Punnett, Sc.D.
University of Lowell
Department of Work Environment
One University Avenue
Lowell, Massachusetts 01854-2881

Program Area: *Musculoskeletal Injuries*
Grant Number: *5 R03 OH02689-02*
Start & End Dates: *08/15/89 - 08/14/91*
Funding Level: *$26,100 ($52,200 Cum)*

Importance to Occupational Safety and Health

Musculoskeletal disorders are a widespread cause of impairment and disability in labor-intensive occupations. Limited epidemiologic evidence has linked upper extremity soft tissue disorders (UESTDs) such as carpal tunnel syndrome (CTS) and tendinitis to occupational ergonomic stressors. The vast majority of the epidemiologic research conducted on work-related musculoskeletal disease to date has been cross-sectional. The "healthy worker survivor effect" is believed to result in an underestimation of work-related increases in risk. Also, prospective data on the conditions under which episodic pain persists or remits is needed for adequate evaluation of the effect of exposure and design and interpretation of intervention studies.

With respect to the definition of endpoints, several of the commonly used UESTD physical examination maneuvers have been shown to lack high sensitivity and specificity. Reproducibility among examiners has not been well studied. Since few objective diagnostic methods are feasible for large-scale screening, it will be valuable to determine whether testing two-point discrimination ability of the fingertips might be a measure of sensory nerve function that could be easily used in the field setting.

Lastly, wage systems in which workers are paid per unit of production are believed to induce a very rapid work pace compared with hourly wage systems. The information in this study on hours worked and earnings will be used to examine whether there was a cross-sectional association between upper extremity pain and work pace (measured as average hourly output) among piece-rate workers.

Objectives

Using data from a longitudinal study of workers occupationally exposed to ergonomic stressors in the garment industry, the objectives of this study are:

1. To estimate the 24-month cumulative incidence of upper extremity musculoskeletal disorders among garment workers previously pain-free, as a function of exposure to occupational ergonomic stressors; and to estimate the long-term and short-term persistence of pain and physical findings and the complementary recovery rates, again in relation to ergonomic exposures, among those workers previously symptomatic.
2. To estimate the magnitude of the selection bias resulting from loss to follow-up, specifically if workers with pain related to occupational exposure(s) are more likely to leave employment than workers not so exposed.
3. To estimate the agreement between two-point discrimination testing for median nerve impairment and other symptoms and signs of carpal tunnel syndrome.
4. To estimate the reproducibility between two examiners of UESTD findings obtained by

physical examination (including two-point discrimination).

5. To explore whether there is an association between upper extremity pain and work pace under the piece-rate system.

Methodology

In 1981-82, baseline prevalence data were collected on symptoms and signs of upper extremity disorders among 207 workers in a women's garment manufacturing shop north of Boston. Cases were defined as persistent pain on standardized questionnaire, with or without physical findings on examination. Selected stitching tasks were identified for detailed ergonomic analysis of work cycle length and frequency of non-neutral wrist and arm postures. The cross-sectional findings have been reported previously.

Follow-up data on the same population are now being analyzed. At 24 months from baseline, 198 active workers were surveyed for symptoms and signs of UESTDs, including about 70% of the 188 members of the original study population. Two-point discrimination testing for median nerve impairment was added to the survey protocol. Thirty months after baseline, data on symptoms and signs were obtained from 46 (90%) of the 51 workers who had been symptomatic at 24 months. The physical examinations were conducted separately by two investigators, the second being blinded with respect to the results of the first.

For those workers studied both in 1981 and 1983, the 24-month cumulative incidence of upper extremity disorders has been estimated by job and will also be estimated for quantitative measures of ergonomic stressors (cycle time and frequency of postures). Among the workers who reported pain, the 24-month and 6-month persistence of and recovery from pain has also been estimated by job category and will be calculated by exposure level. The probability of remaining employed over 24 months has been calculated conditional on the presence or absence at baseline of UESTD symptoms or symptoms plus signs, to estimate the magnitude of the selection bias resulting from loss to follow-up.

Findings will be compared between the physical examinations of the two examiners and between the two-point discrimination test for median nerve impairment, and other signs of CTS will be computed. The same statistics will also be calculated after stratifying on severity of symptoms, to determine if more severe pain is associated with reproducibility of any single test or with agreement among the carpal tunnel test procedures.

Timesheets were also obtained containing data for all employees on hours worked, wage basis (hourly or piece-rate), and earnings for one week when the health data were collected. These data permit the examination of a possible cross-sectional relationship between upper extremity pain and work pace as measured by production. Internal comparisons have been made within piece-rate jobs to compare cases and non-cases on average hourly output.

Significant Findings

The cross-sectional prevalence estimates in the second survey were of comparable magnitude to the estimates previously obtained. The rates of transition between the states of being pain-free and having persistent musculoskeletal pain have been estimated. In the analysis to date, there is little evidence that garment workers with pain at baseline were less likely to remain employed two years later than workers pain-free at baseline. There is also no evidence of a cross-sectional relationship between work pace and prevalence of upper extremity pain among piece rate workers.

Kinematics and Kinetics of the Pull Phase of Lifting

Mohamed M. Ayoub, Ph.D.
Texas Tech University
Department of Industrial Engineering
P.O. Box 4130
Lubbock, Texas 79409-3061

Program Area: *Musculoskeletal Injuries*
Grant Number: *1 R03 OH02763-01*
Start & End Dates: *07/01/90 - 06/30/91*
Funding Level: *$19,100 ($19,100 Cum)*

Importance to Occupational Safety and Health

The National Institute for Occupational Safety and Health Lifting Guide (NIOSH, 1981, p. 40) states that "dynamic forces imparted by rapid or jerky motions can multiply the load's effect greatly," and recommends that manual materials handlers lift the load in a smooth and deliberate manner. However, it is suspected that the human operator must lift in a manner which causes peak forces applied by the hands to the load, resulting from a jerking motion, to overcome the inertia of the box

resting on the ground. Therefore, smooth and controlled lifting may not be a realistic recommendation. The application of knowledge of the peak applied forces is useful for a biomechanical re-evaluation of lifting tasks, and for the establishment of the point of time in the lift and associated posture when L5/S1 compression and shear forces may limit lifting capacity.

Objectives

The first objective of the research is to directly measure applied forces by the hands to a load from floor to knuckle height, and compare these to predictions by biomechanical models such as DYNALIFT. If necessary, the dynamic model will be supplemented by a static biomechanical model to account for forces on the hands during the pull phase of the lift, namely as the inertia of the load is picked up. The project's second objective is to determine the effects of fast and slow lifting speeds and percent of Maximum Acceptable Weight of Lift (MAWL) on the external forces applied by the hands to the load during the pull phase of lifting from floor to knuckle height. Blocked factorial designs will be used to analyze the effects of absolute weight, %MAWL, and speed of lift on peak forces applied by the hands to the load during the pull phase of lifting from floor to knuckle height.

Methodology

In order to achieve the objectives of the project, a container with handles was designed and fabricated. The handles were instrumented to measure the vertical and fore-aft forces applied by the lifter on the container. The forces were measured using strain gauges mounted on the handles. This system was calibrated prior to use in the experiment. For this experiment a design calling for 5 male subjects was established. Each subject participated in a task familiarization period (two days, two hours/day). The experimental design was a split plot design using subjects as blocks. The independent variables used were lifting speeds (two levels), lifting frequency (three levels), and weight lifted (35%, 60%, and 85% of MAWL). Dependent variables selected were (a) magnitude of peak forces applied to the handles in vertical and horizontal directions, (b) maximum compressive forces on L5/S1, and (c) maximum shear forces on L5/S1.

Significant Findings

Preliminary data suggest that significant forces are applied to the handles to overcome the inertia of the load. Therefore, lifting smoothly does not appear to be a possible option. This means that a jerky movement is necessary to start the load in motion. These forces are important, for they significantly increase the compression and shear forces on the spine. From the preliminary data collected, it appears that these forces are approximately 2.3 times the load for normal lifting speeds and increase to 3.5 times the load for fast lifting speeds.

Occupational Epidemiology of Carpal Tunnel Syndrome

Hal Morgenstern, Ph.D.
UCLA School of Public Health
Department of Epidemiology
10833 Le Conte Avenue
Los Angeles, California 90024-1772

Program Area: *Musculoskeletal Injuries*
Grant Number: *1 R03 OH02765-01*
Start & End Dates: *09/28/90 - 09/27/92*
Funding Level: *$22,181 ($22,181 Cum)*

Importance to Occupational Safety and Health

Cumulative trauma disorders (CTDs) are one of the most commonly reported occupational health problems in today's working environment. The number of worker compensation claims filed for these disorders increased tremendously during the 1980s. Carpal tunnel syndrome (CTS) is the most commonly reported cumulative trauma disorder. Although CTS has been widely recognized as a clinical syndrome for many years, there are few studies that have examined CTS utilizing rigorous epidemiologic methods. This research will examine the magnitude of CTS among selected occupational groups which to date have received little epidemiologic attention. These occupational groups are office workers, court reporters, carpenters, and sprinkler fitters. The information derived from this research will be useful in assessing the magnitude of CTS in these occupations and for identifying occupational risk factors for CTS that might be incorporated into prevention strategies for the workplace.

Objectives

The primary objective of this research is to provide epidemiologic information regarding the prevalence of CTS among occupational groups for which there is a paucity of epidemiologic data. In addition to examining occupational factors associated with CTS prevalence, other objectives of this project are to examine the "healthy worker effect" with respect to CTS in the selected occupations, to estimate the effects of other factors on CTS occurrence such as psychosocial factors, past medical history, and personal life style factors. Another objective is to evaluate diagnosis-related issues of CTS through a comparison of electrodiagnostic findings, objective clinical signs, and symptom reporting.

Methodology

The study design for this project involves two phases: a cross-sectional survey and a nested case--control study of 100 cases and 100 controls selected from the cross-sectional survey population. In the cross-sectional phase, about 4,000 members from three selected unions, representing office workers, court reporters, carpenters, and sprinkler fitters, will receive a self-administered questionnaire. These members will be randomly selected from union rosters provided by three Los Angeles area unions: Service Employees International Union (Local #660), the Carpenters Union (Local #409), and the Sprinkler Fitters Union (Local #709).

The data that will be obtained in the cross-sectional survey questionnaire and the case-control interview include information on socio-demographic factors (age, race, sex, education, marital status), occupational history (current occupation, job task information, psychosocial factors of work), medical and physical information (history of traumatic injury, reproductive history, selected medical diagnoses and conditions, current height and weight, and handedness), CTS symptoms and related factors (pain, numbness, tingling and weakness in hands and wrist, use of medical care for symptoms, and symptoms' impact on work and leisure activities), other symptoms (pain in other areas of the body), and behavioral/leisure activities (smoking history, leisure activities).

In the case-control phase, participants will also receive electrodiagnostic testing (distal sensory and motor latencies of the median nerve), clinical exams (Phalen's test, Tinel's test, and measurements of wrist size and dimensions), and a personal interview. The case-control interview includes more extensive questions on CTS symptoms, medical history, and occupational work task information. Cases are selected on the basis of their reporting of CTS symptoms in the cross-sectional survey; controls will be selected among those who do not report nocturnal pain or symptoms localized in the distribution area of the median nerve. Controls will be matched to cases by age, sex, and occupation.

Significant Findings

None to date.

Sudden Loading and Fatigue Effects on the Human Spine

Daniel R. Baker
The University of Utah
Department of Mechanical Engineering
2266 MEB
Salt Lake City, Utah 84112

Program Area: *Musculoskeletal Injuries*
Grant Number: *1 R03 OH02821-01*
Start & End Dates: *09/28/90 - 09/27/91*
Funding Level: *$14,967 ($14,967 Cum)*

Importance to Occupational Safety and Health

This research is examining the effects of dynamic loading and fatigue on the lower back by utilizing models of muscle response, body motion, and disc compression. Knowing the dynamic musculoskeletal response as a function of a person's loading and level of fatigue will enable researchers and clinicians to better examine and treat some of the basic causes of low back pain. This, in turn, may help predict and thereby reduce possible back problems of workers who are performing dynamic balance tasks for long periods of time.

Objectives

Torso and torso muscle response to a sudden (impulsive) load will be determined under rested and fatigued conditions. It is expected that the control strategies utilized by the subject will change or be significantly altered when the fatigue condition is compared to the rested condition. Further analyses will indicate how much worse dynamic loading under fatigued conditions is on the low back than when it is in a rested state. Finally, torso and muscle response parameters will be determined experimentally for each subject.

Methodology

The Torso Motions Measurement System (ToMMS) was developed as an *in vivo* test device for gathering data according to theoretical torso models based on the inverted pendulum problem (how to balance a broomstick held upside-down in one's hand so that it does not fall). The subjects will be constrained such that the only motion they can perform will be anterior-posterior rotations about the L5/S1 joint (and some bending along the spinal column which will be simultaneously measured). Several impulse loads will be administered and the motions of the subject tracked using the ToMMS. The subject will then be taken through a series of graded exercises which increase the subject's muscular fatigue to a predetermined level, and he/she will be retested.

Significant Findings

None to date.

Occupational Cancer Surveillance: New Approaches

G. Marie Swanson, Ph.D., M.P.H.
Michigan State University
Cancer Center
A211 East Fee Hall
East Lansing, Michigan 48824-1316

Program Area: *Occupational Cancers*
Grant Number: *5 R01 OH02067-07*
Start & End Dates: *09/30/88 - 09/29/91*
Funding Level: *$152,499 ($1,079,044 Cum)*

Importance to Occupational Safety and Health

The Occupational Cancer Incidence Surveillance Study (OCISS) will contribute to the reduction of morbidity and mortality due to occupational risk factors for eleven types of cancer. It is developing both methodologic and substantive leads that will be useful for direct prevention programs as well as for further research. Findings to date indicate that important new information is being gained regarding the occupational cancer risks of blacks and women, in particular. The significance of leads regarding occupational cancer risks among blacks and women cannot be overemphasized; as to date, more than 95% of occupational cancer epidemiology has included white males only. One analytic study (investigating familial risk of lung cancer among non-smokers identified by OCISS and utilizing the same questionnaire to obtain smoking and occupational histories among family members) has been launched from OCISS that would not have been feasible otherwise. Others will follow. Furthermore, OCISS data have contributed to the methodology of occupational epidemiology, having demonstrated that occupational information from death certificates, when contrasted to that obtained from OCISS interviews, produces substantial error in the estimates of occupational risk. The penultimate objective is to design studies aimed at identifying specific carcinogens. Ultimately, cancer prevention programs in the workplace will be developed.

Objectives

The long-term goal of this study is to develop and test new hypotheses regarding the occupational etiology of selected forms of cancer. Both cancer incidence data, as the disease outcome measures, and lifetime work histories will be utilized, complemented by other essential risk factor data associated with the measures of exposure.

The specific aims of this study are:

1. To determine risks by occupation and industry for black and white males and females in conjunction with detailed tobacco smoking history, socioeconomic status, and age at diagnosis by cancer type.
2. To determine cancer risk within specific occupations in major local industries, such as automobile manufacturing, construction, machinery manufacturing, and primary ferrous metals manufacturing.
3. To investigate work-related cancer risk by race, gender, socioeconomic status, age at diagnosis, and cancer site among persons who have never smoked cigarettes, pipes, or cigars.
4. To develop new methodologic approaches for occupational epidemiology.

Methodology

This study utilizes a case-referent design, comparing the prevalence of occupational risk factors among cancer cases (lung and bronchus, urinary bladder, esophagus, liver, salivary glands, eye, mesothelioma, stomach, or cutaneous melanoma) with those of a referent group, which includes persons diagnosed with cancers of the colon or rectum. Cancer cases are selected from the Metropolitan Detroit Cancer Surveillance System (MDCSS), a population-based cancer registry which has been in operation since 1969. Interviews are conducted by telephone and include lifetime health histories, work histories, tobacco use histories, and socioeconomic information.

Significant Findings

Analyses of lung and bronchus cancers are producing exciting new findings. Assessment of lung and bronchus cancer risk by usual occupation and industry was completed in June of 1990. A manuscript describing these findings was accepted by the American Journal of Industrial Medicine on October 3, 1990. This study is the first to show an increased risk of lung cancer among farmers, after adjusting for cigarette smoking habits and age at diagnosis. Other new discoveries from this analysis include the observation that increased risk of lung cancer among mechanics is restricted to black males. Further, we found that black males had higher Odds Ratios when their usual occupation was military service (OR= 11.0) than was seen among

white males (OR=4.0). Recent studies suggest that exposure to diesel exhaust may increase lung cancer risk, but there are contradictory findings from various investigations into this question. In our analyses, five occupations that are known to have diesel exhaust exposure had significantly elevated Odds Ratios, and these Odds Ratios were highest among the occupations most likely to have the greatest levels of diesel exhaust exposure (mining machine operators, OR=5.03; driver sales, OR=2.39; farmers, OR=2.36; truck drivers, OR=2.31; and mechanics, OR= 1.72). We also observed that persons working in the primary ferrous manufacturing industry, in coal mining, and in the Armed Services have elevated risk of lung cancer, after adjusting for cigarette smoking habits.

Analyses are nearly complete to assess length of employment and lung cancer risk. These analyses provide some of the first insights into occupational cancer risks among black males. For example, we observed that increasing lung cancer risk for increasing years of employment for black males occurs in the occupations of automobile mechanic and tool and die maker and in the industries of coal mining, primary ferrous metals manufacturing, automobile repair, security guards, hospitals, and food processing. Elevated risks also have been shown for women and for white males.

Analyses of usual occupation and industry and risk of cancer of the urinary bladder is being completed. Findings from this analysis show the importance of including data concerned with cigarette smoking habits in studies of occupational bladder risks, since bladder cancer patients who smoked cigarettes have 3- to 4-fold elevated risks of bladder cancer. Analyses of workplace risks among bladder cancer patients revealed the following occupations and industries to be associated with elevated levels of bladder cancer, after adjusting for cigarette smoking habits, age at diagnosis, race, and gender: construction administration, precision workers, health technicians, welders, automobile sales, production supervisors, telephone installers, electricians, postal clerks, Armed Services personnel, hardware sales, and meat manufacturing.

Publications

Burns PB, Swanson GM: The Occupational Cancer Incidence Surveillance Study (OCISS): Risk of Lung Cancer by Usual Occupation and Industry in the Detroit Metropolitan Area. American Journal of Industrial Medicine, in press, 1990

Schade WJ, Swanson GM: A Comparison of Death Certificate Occupation and Industry Data with Lifetime Occupational Histories Obtained by Interview: Variations in the Accuracy of Death Certificate Entries. Am Ind Med 14:121-136, 1988

Illis WR, Swanson GM, Satariano ER, Schwartz AG: Summary Measures of Occupational History. A Comparison of Latest Occupation and Industry with Usual Occupation and Industry. Am J Public Health 77:1532-1534, 1987

Swanson GM, Schwartz AG, Brown KL: Population-Based Occupational Cancer Incidence Surveillance--Utilization of the Telephone Interview. J of Occup Med 27:439-444, 1985

Swanson GM, Schwartz AG, Burrows RW: An Assessment of Occupation and Industry Data from Death Certificates and Hospital Medical Records for Population-based Cancer Surveillance. Am Ind Med 74:464-467, 1984

Relative Health Risks of Diesel Emission Control Systems

Susan T. Bagley, Ph.D.
Michigan Technological University
Department of Biological Sciences
Houghton, Michigan 49931

Program Area: *Occupational Cancers*
Grant Number: *5 R01 OH02611-02*
Start & End Dates: *01/01/89 - 12/31/91*
Funding Level: *$87,311 ($169,304 Cum)*

Importance to Occupational Safety and Health

Whole diesel exhaust is regarded as a potential occupational carcinogen by the National Institute for Occupational Safety and Health (NIOSH), but the risk of cancer to exposed workers has not been quantitatively defined. One problem encountered in defining risk is the chemical complexity of diesel exhaust, making it difficult to define exposure. Michigan Technological University (MTU) and the Bureau of Mines (BOM) are working together to define key aspects of the chemical nature and biological activity of diesel particulate matter (DPM) collected in underground mines and DPM and semi-volatile organics collected from a heavy-duty diesel engine operated with and without emission control devices in the laboratory. Together, these data will help evaluate the potential health effects of diesel exhaust and the impact of

emission control devices on the underground mine environment.

Objectives

The objectives of this project are: (1) to obtain estimates of diesel pollutant levels in underground coal mines, to include polynuclear aromatic hydrocarbons (PAH) and biological activity, and (2) to assess the effects of using DPM emission control systems on these pollutants in laboratory tests.

Methodology

Samples from four underground coal mines were collected by BOM personnel using Hi-volume samplers equipped with inertial impactors to collect size-differentiated particle samples. Particles $\geq 1\ \mu m$ in size were considered to be primarily of diesel origin. A sampler was located at the section intake and operated up to six hours per sample. Another Hi-volume sampler was placed in the haulageway near the point where diesel shuttle cars turned around to dump their loads. The sample times for these samples varied between 8-30 minutes and were only collected during periods when mining and diesel activity were occurring. The soluble organic fraction (SOF) was removed from the particles on the filters by Soxhlet extraction with dichloromethane. The daily extracts from all filters at each sampling location in a mine were pooled to reflect average levels over each day's sampling period.

Laboratory samples for DPM and semi-volatile organics were collected by the BOM with and without a catalyzed diesel particulate filter (CDPF) on 508 x 508-mm filters followed by XAD-2 resin (XOC) during transient engine operation. Only particle samples were collected during steady-state operation. This engine was operated with low sulfur (0.039 wt. %) fuel. As with the in-mine samples, the organic material associated with both types of media was removed by Soxhlet extraction with dichloromethane.

PAH and nitro-PAH fractions of the SOF and XOC were obtained from a two-column clean-up procedure and analyzed by HPLC with fluorescence detection. The PAH and nitro-PAH chosen for quantitation due to their known or suspected health effects include fluoranthene, chrysene, benz[a]anthracene, benzo[a]pyrene, 1-nitropyrene, 2-nitrofluorene, and 3-nitrofluoranthene. Sulfate levels are determined by ion chromatography of aqueous extracts from the filters following their Soxhlet extraction for SOF removal. Unfractionated extracts plus some fractions are tested for biological activity using the microsuspension version of the Ames assay. Coal samples from each mine are also extracted and assayed for PAH levels and activity. The data from the laboratory generated samples were converted to estimated in-mine concentrations in order to better evaluate potential impacts of certain engine operating conditions and emission control systems.

Significant Findings

Wide variations in some of the measured parameters have been found between the underground coal mines. Up to 20-fold differences were found in DPM, SOF, mutagenicity, and PAH values in the intake samples at the four mines, probably due to the random operation of diesel support vehicles operating upstream from the Hi-volume sampler. In contrast, eight-fold or less differences in the same parameters were found at the haulageway sites, perhaps due to the collection of these samples only when diesel activity was present. For all mines, the intake DPM and SOF concentrations were from 5 to 30% of the haulageway mean values of 0.75 to 1.9 mg/m^3 and 0.12 to 0.40 mg/m^3, respectively. These haulageway DPM concentrations are similar to those found at the same mines using personal diesel exhaust aerosol samplers. DPM-associated mutagenicity at the intake was about 33% of the mean haulageway values of 440 to 970 revertants/m^3 due to differences in DPM composition and levels between the sampling sites. Mean intake PAH concentrations at three of the mines varied from 9 to 60% of the haulageway values. Examples of mean haulageway DPM-associated PAH concentration ranges (ng/m^3) are 48 to 390 for fluoranthene, 34 to 270 for pyrene, and < 0.9 to 61 for benzo[a]pyrene. The PAH concentrations and mutagenicity levels are generally within the broad ranges reported for other types of dieselized underground mines. The intake DPM was apparently from out-by diesels and probably contributed to the variation found with the haulageway samples. Differences in the types of engines in use at each mine and/or how the diesels were operated and maintained probably accounts for much of the between-mine differences.

Extracts of coal samples from each mine were analyzed and found to contain very low levels of extractable organics and PAH and no mutagenic activity. Submicrometer coal particles should contribute $\leq 5\%$ of the mass, none of the mutagenicity, and $\leq 0.2\%$ of the PAH levels.

A comparison was made of the diluted laboratory-generated data (with no control device) to the actual values measured at the haulageway

sites using an in-mine dilution ratio of 100:1. These diluted laboratory-generated data for DPM, SOF, mutagenicity, and PAH concentrations were not found to be statistically different ($p = 0.05$) from the data from most of the mines. When the potential 20:1 - 200:1 in-mine dilution ratio range was examined, the laboratory data bracketed virtually all of the observed in-mine data. This indicates that laboratory-generated diesel emission data are useful in estimating in-mine levels.

The effect of the CDPF over transient operation was to reduce DPM, SOF, and XOC concentrations by about 90, 98, and 82%, respectively. A similar reduction in SOF was found with steady-state operation; however, time-weight DPM levels were reduced by only 47%. Increases in sulfate levels of 550 and 1200% during transient and steady-state operation, respectively, accounted for much of the differences in CDPF effects on DPM and SOF. SOF-associated mutagenicity (revertants/ug) increased from 300 to 3300% with CDPF use under transient and steady-state conditions, respectively; due to the major effect of the CDPF on SOF concentrations, the mutagenic concentrations (revertants/m^3) decreased by about 90%. In comparison to the SOF, the XOC was only weakly mutagenic and CDPF use resulted in reductions in activity on a mass basis of 40% and on a concentration basis of 91%. Use of the CDPF resulted in approximately 99% decreases in concentrations of PAH such as fluoranthene, pyrene, and benzo[a]pyrene. Based on completed analyses, in-mine DPM concentrations with the CDPF installed would be below 0.1 mg/m^3, representing at least 10-fold reductions in DPM. Similar reductions would also be expected in DPM-associated mutagenicity and PAH concentrations.

Biologic Monitoring/Risk Assessment in an Exposed Cohort

George P. Hemstreet, III, M.D.
The University of Oklahoma Health Sciences Center
Department of Urology
P.O. Box 26901
Oklahoma City, Oklahoma 73190

Program Area: *Occupational Cancer*
Grant Number: *3 R01 OH02647-01S1*
Start & End Dates: *09/30/89 - 10/30/92*
Funding Level: *$153,295 ($183,710 Cum)*

Importance to Occupational Safety and Health

Thousands of workers worldwide are at increased risk of bladder cancer because of previous exposure to aromatic amines. These risks have been characterized in the past primarily by epidemiologic means, permitting assessment of risks associated with the cohort as a whole. If markers within the cancer process can be identified, individuals in the exposed cohorts might be differentiated according to risk and targeted for the appropriate intervention. In addition to occupational chemical exposure, other exogenous risk factors and endogenous risk factors influence the estimated relative risk or overall odds of the individual developing bladder cancer. Data on the prevalence of various risk factors and biological markers in exposed cohorts could be used to develop individual risk profiles which could be helpful for determining individual risk in other high-risk cohorts identified by epidemiologic means.

Results of the pilot study and this larger study of identified high-risk cohorts in China could provide significant new data on early detection of bladder cancer, exogenous and endogenous risk factors associated with the disease, and biological intermediate endpoint markers indicative of bladder cancer risk. These findings could have profound implications for the development and initiation of bladder cancer screening programs in the large number of U.S. industries in which workers are or have been exposed to bladder carcinogens.

Objectives

The purpose of the pilot study was to demonstrate the feasibility of conducting the screening program in China and to confirm the

logistics of the handling and shipment of samples for laboratory studies in the U.S. The objectives of the larger study are: (l) to identify and measure the various endogenous and exogenous risk factors and biological markers in order to differentiate individuals and subgroups according to their risk for bladder cancer, and (2) to evaluate the usefulness of various biological markers as discriminators of risk and as intermediate endpoint markers.

Methodology

In the pilot study, 30 members of a previously identified cohort of workers (N=2,005) exposed to benzidine and an equal number of unexposed controls were screened. All subjects in the pilot study were from the Tianjing province in China.

The objectives of the screening, relative to the following, are: (1) exogenous risk factors - characterize each study subject on the basis of personal medical history, family medical history, occupational exposure to benzidine or other bladder carcinogens, and cigarette smoking history; (2) endogenous risk factors - determine whether the slow acetylator phenotype or urinary pH is predictive of risk for bladder cancer or for urinary cytologic abnormalities; and (3) biological markers - determine the prevalence of specific biological markers, i.e., morphologic changes identified by Papanicolaou cytology and biochemical and morphologic changes identified by quantitative fluorescence image analysis (QFIA) cytology, and correlate these with each other and with exogenous and endogenous risk factors to determine which best discriminate individuals and subgroups at risk for bladder cancer. Included among QFIA analyses are: DNA hyperploidy, F-actin levels in cells, labeling with an antibody against a tumor-related antigen found in low-grade tumors, and selected oncogene protein levels.

The initial screening phase includes: standardized interviews to obtain occupational, smoking, personal medical and family medical histories, limited physical examinations performed by a urologist, and collection of voided urine and blood samples. Diagnostic follow-up is included for subjects whose initial screening results meet certain criteria.

Significant Findings

The pilot study demonstrated that an excellent cohort is available for the study, with good compliance and participation. Adequate histories and physical and laboratory data can be collected and analyzed to determine endogenous and exogenous risk factors. The data base format was established and an analysis completed. Acetylator phenotypes must be determined by the caffeine analysis method because of difficulty in obtaining more than a single blood sample. The Chinese staff performed very well in data recording and entry.

Significant advances have been made in determining multiple markers on the same cell. We can now perform quantitative DNA, qualitative markers on tumor-associated antigens, and quantitation of one other marker on the same cell, which will aid in further defining the sequence of events in the oncogenic process, provide a means to deal with the problem of heterogeneity, and potentially improve both sensitivity and specificity of cancer detection and risk prognostication. Both endogenous and exogenous risk factors can be obtained on this well-defined cohort. Participation of cohort members was excellent, but control group compliance was poor, so we must include more controls. Follow-up of the subjects with positive QFIA cytologies includes the collection of bladder wash samples, providing a field test of the collection and shipping of such samples. Availability of additional markers may suggest altering the criteria for follow-up.

Publications

Rao JY, Hurst RE, Bales WD, Jones PL, Bass RA, Archer LT, Hemstreet GP: Cellular F-actin Levels as a Marker for Cellular Transformation: Relationship to Cell Division and Differentiation. Cancer Research 50(8):2215-2220, 1990

Jones PL, O' Hare CM, Bass RA, Rao JY, Hemstreet GP, Hurst RE: Quantitative Immuno-fluorescence, Anti-ras p21 Antibody Specificity, and Cellular Oncoprotein Levels. Biochem Biophysical Research Communications 167(2):464-470, 1990

Hurst RE, Jones PL, Rao JY, Hemstreet GP: Molecular and Cellular Biological Approaches and Techniques in the Detection of Bladder Cancer and Enhanced Risk for Bladder Cancer in High Risk Groups. J Occ Med 32(9):854-862, 1990

Hemstreet GP, Hurst RE, Bass RA, Rao JY: Quantitative Fluorescence Image Analysis in Bladder Cancer Screening. J Occ Med 32(9):822-828, 1990

Rao JY, Hemstreet GP, Hurst RE, Bass RA, Min KW, Jones PL: Cellular F-actin Levels as a Marker for Cellular Transformation: II. Relationship to DNA Ploidy and Cytology in Diagnosis and

Prediction of Bladder Cancer Risk. Cancer Research, accepted for publication, 1990

Rao JY, Hemstreet GP, Min KW, Hurst RE: F-Actin Levels As A Quantitative Marker for Bladder Cancer Risk. Poster, Annual Meeting, American Urological Association, Inc., New Orleans, LA, May 13-17, 1990. J Urol 143(4):405A, 1990

Hemstreet GP, Bass RA, Rao JY, Min KW, Hurst RE: Tumor Associated Antigens for Detecting Low Grade Bladder Cancer. Poster, Annual Meeting, American Urological Association, Inc., New Orleans, LA, May 13-17, 1990. J Urol 143(4):325A, 1990

Case Control Study of Cancer in Synthetic Rubber Workers

Genevieve M. Matanoski, M.D., Dr.P.H.
The Johns Hopkins University
School of Hygiene and Public Health
615 North Wolfe Street
Baltimore, Maryland 21205

Program Area: *Occupational Cancers*
Grant Number: *1 R01 OH02730-01*
Start & End Dates: *06/01/90 – 05/31/92*
Funding Level: *$331,603 ($331,603 Cum)*

Importance to Occupational Safety and Health

Butadiene is the 36th most common chemical produced in the U.S. (IARC, 1986). It is used in the making of plastics, resins, rocket fuels, and rubber and rubber products. Animal studies suggest that the chemical is carcinogenic - at different sites depending on dose - and it also has the unusual property of activation of retroviruses. The International Agency for Research on Cancer considered the chemical to be "possibly carcinogenic."

In the 1950s and 1960s, toxicologists tested some of the metabolic byproducts of 1,3-butadiene and found them to be carcinogenic in mice and rats. Species differences in metabolic pathways and in the rate of concentration may have played a role in the differences in incidence of cancers found in these animal studies.

Although the risk of cancer associated with work in the rubber industry has been recognized for many years, few studies of health effects from rubber polymerization have been done. In the 1970s, concern about styrene-butadiene rubber polymer production centered primarily around the use of styrene. Results of studies in the late 1970s and early 1980s suggested that styrene might not be the chemical which was related to observed cancer risks.

Some studies of humans have been done; however, more work is needed to identify human risks from butadiene and potential interactions between styrene and butadiene. Since animal data suggest effects at very low levels, human data are needed to help identify the appropriate level for a new industry standard. The differences in metabolism of the chemicals by species makes it important to have data on health effects related to dose in humans. This study will emphasize human effects from exposure to butadiene based on industrial monitoring measures to determine risk by dose.

Objectives

The goals of this research are to examine the risk of mortality from lymphopoietic, hematologic, and gastrointestinal cancers and sarcomas from occupational exposure to butadiene and styrene and to determine if a dose response exists.

Methodology

The study consists of three components: (1) A nested case-control study of selected cancers to determine the association between exposure to butadiene and styrene and risk of specific cancers. (2) A characterization of exposure by jobs using measured levels of butadiene and styrene, the comparison of these measured levels to the estimated relative ranks used in earlier studies, and the use of both the actual measures and the estimated measures in the case-control study. (3) An expansion of the original cohort of workers studied earlier to include short-term workers for mortality analysis and for addition to the nested case-control study.

Significant Findings

None to date.

New Method for Occupational Cancer Surveillance

Paul W. Brandt-Rauf, Sc.D., M.D.
Columbia University
School of Public Health
Division of Environmental Sciences
60 Haven Avenue, B-1 Level
New York, New York 10032

Program Area: *Occupational Cancers*
Grant Number: *5 K01 OH00076-02*
Start & End Dates: *07/15/89 – 07/14/92*
Funding Level: *$37,714 ($70,028 Cum)*

Importance to Occupational Safety and Health

An important goal of occupational health is the prevention of occupational cancers. A critical step toward that goal is the development of biomarkers of exposure and response to workplace carcinogens. Such biomarkers should allow identification of those individuals who are at an early stage of developing neoplastic disease so that the disease process can be aborted. This research proposes to demonstrate the utility of a newly developed biomarker, based on the detection of oncogene-encoded proteins in serum, in contributing to the early detection of biological response to workplace carcinogen exposure.

Objectives

The overall aim of this research is to develop monoclonal antibody immunoblotting assays for the detection of oncogene protein products in serum that could be used to screen for early neoplastic changes in occupational cohorts at risk for malignant disease due to workplace exposures. This approach is based on the hypothesis that many occupational carcinogen exposures presumably produce cancer via a pathway that includes oncogene activation at a relatively early stage, a hypothesis for which there is already considerable experimental support.

Methodology

The research consists of two parts. The first will involve validation of the serum oncogene protein assay in cohorts of cancer patients (including cancers of occupational concern such as lung cancer) with known oncogene activation and in matched controls. Sensitivity, specificity, and reproducibility of the test will be determined, and the seroprevalence of specific oncogene products among patients with various types and stages of cancer will be demonstrated. The second part will involve an attempt to estimate the predictive value of this assay in determining those individuals who will get cancer in occupational cohorts with potential carcinogen exposure and potential increased risk of malignancy (asbestos workers, firefighters) in a nested case-control study based on banked sera specimens.

Significant Findings

Thus far, preliminary results on cancer patients and controls indicate this assay to be highly sensitive, specific and reproducible. In addition, positive results have been identified in the occupational cohorts, but the significance of these findings is unknown as yet since the samples are being assayed blind and the identification code will not be broken until the conclusion of the study.

Publications

Perera F, Mayer J, Santella RM, Brenner D, Jeffrey A, Latriano L, Smith S, Warburton D, Young TL, Tsai WY, Hemminki K, Brandt-Rauf PW: Biologic Markers in Risk Assessment for Environmental Carcinogens. Environmental Health Perspectives, in press, 1990

Perera FP, Jeffrey AM, Brandt-Rauf PW, Brenner D, Mayer JL, Smith SJ, Latriano L, Hemminki K, Santella R: Molecular Epidemiology and Cancer Prevention. Cancer Detection and Prevention, in press, 1990

Brandt-Rauf PW: Serum Screening for Oncogene Proteins in Occupationally Exposed Workers. Journal of Cancer Research and Clinical Oncology 116:982, 1990 (Abstract)

Perera F, Fischman HK, Hemminki K, Brandt-Rauf PW, Niman HL, Smith S, Toporoff E, O'Dowd K, Tang MX, Tsai WY, Stoopler M: Protein Binding, Sister Chromatid Exchange and Expression of Serum Oncogene Proteins in Patients Treated with Cisplatinum (cisDDP)-based Chemotherapy. Archives of Toxicology 64:401-406, 1990

Brandt-Rauf PW, Niman HL, Smith SJ: Correlation Between Serum Oncogene Protein Expression and the Development of Neoplastic Disease in a Worker Exposed to Carcinogens. Journal of the Royal Society of Medicine 83:594-595, 1990

Brandt-Rauf PW: Oncogene Proteins as Molecular Epidemiologic Markers of Cancer Risk in Hazardous Waste Workers. Occupational Medicine: State of the Art Reviews 5:59-65, 1990

Perera F, Jeffrey A, Santella RM, Brenner D, Mayer J, Latriano L, Smith S, Young TL, Tsai MY, Hemminki K, Brandt-Rauf PW: Macromolecular Adducts and Related Biomarkers in Biomonitoring in Epidemiology of Complex Mixtures. In: Complex Mixtures and Cancer Risk, (eds. H Vainio, M Sorsa, AJ McMichael), IARC Scientific Publications No. 104, IARC, Lyon, pp. 4-180, 1990

Brandt-Rauf PW, Smith S, Perera FP: Molecular Epidemiology and Environmental Carcinogenesis of the Lung. Problems in Respiratory Care 3:44-61, 1990

Brandt-Rauf PW, Smith S, Niman HL, Yohannan W, Hemminki K, Perera F, Santella R: Serum Oncogene Proteins in Foundry Workers. Journal of the Society of Occupational Medicine 40:11-14, 1990

Brandt-Rauf PW: Oncogenes and their Applications in Epidemiologic Studies. American Journal of Epidemiology 131:1099-1100, 1990 (Letter)

Brandt-Rauf PW, Smith S, Niman HL, Goldstein MD: Serum Oncogene Proteins in Hazardous Waste Workers. Journal of the Society of Occupational Medicine 39:141-143, 1989

Leukocyte DNA Adducts after Carcinogen Exposure

Gerald N. Levy, Ph.D.
University of Michigan
Department of Pharmacology
6322 Medical Sciences Building I
Ann Arbor, Michigan 48109-0626

Program Area: *Occupational Cancers*
Grant Number: *1 K01 OH00081-01*
Start & End Dates: *03/01/90 – 02/28/93*
Funding Level: *$46,682 ($46,682 Cum)*

Importance to Occupational Safety and Health

Occupational exposure to carcinogenic chemicals is usually regulated on the basis of measurement of the level of a carcinogen in the workplace. This is a less than ideal method as a specific analytical method is needed for each carcinogen or a "signature" compound is determined as representative of all carcinogens presumably present. There is some question about the relevance of the air or surface concentration of carcinogens to actual worker exposure. A more significant measurement would be the actual absorbed dose for each worker. The work supported by this grant seeks to develop a method for determining the actual amount of carcinogen exposure received by an individual regardless of the dose in the environment, particular work assignment, protective measures taken, or individual genetic makeup.

Objectives

The major goal of this research is to determine if the measurement of DNA-carcinogen adducts in circulating white blood cells can be used as a monitor of *in vivo* exposure to carcinogens. This determination will be made by developing methods of analyzing DNA adducts in white blood cells, investigating the dose-response relationship, and then comparing the levels of leukocyte DNA adducts with DNA-carcinogen adducts found in target tissues of various classes of carcinogens. A secondary goal of the research is to determine if white blood cells have the ability to activate environmental and occupational carcinogens to metabolites capable of forming DNA adducts.

Methodology

All studies will be conducted using inbred mice. DNA will be isolated and purified from white blood cells, liver, and urinary bladder of control and carcinogen treated mice. DNA adducts will be detected and measured by HPLC and scintillation counting after ^{32}P-postlabeling of nucleotides obtained from hydrolysis of the DNA.

Initially, the relationship of dose of carcinogen given to adduct level and that of time after exposure to adduct level will be determined using 2-aminofluorene as a representative carcinogenic arylamine. Subsequently, representatives of other classes of carcinogens such as benzo[a]pyrene as a representative polycyclic aromatic hydrocarbon will be used.

The ability of white blood cells to activate carcinogens will be examined by isolating mouse white blood cells and incubating them with carcinogen for 12 to 24 hours under standard cell culture conditions. The cells will be harvested, DNA prepared, and adducts analyzed by

^{32}P-postlabeling followed by HPLC and scintillation counting.

Significant Findings

Several technical procedures needed to be optimized at the beginning of this project. The method of obtaining usable amounts of uncontaminated blood from individual mice was developed. After trying cardiac puncture after ether anaesthesia or after sacrifice by cervical dislocation, it was decided to use simple tail bleeding after warming the mice in an environmental chamber. This method gives 0.5 to 0.8 ml of uncontaminated blood without undue stress to the mouse. The method of obtaining white blood cell DNA has been improved over what was originally proposed. Instead of a detergent lysis of all the blood cells, we have substituted a freeze-thaw procedure to lyse red cells, followed by washing away most of the released hemoglobin before lysing the white cells. This modification has increased the yield of DNA and improved the quality of the DNA obtained.

At present, leukocyte DNA adducts from a single dose (60 mg/kg) of 2-aminofluorene and a single time point (3 hrs after exposure) have been analyzed by ^{32}P-postlabeling and HPLC. Under these conditions DNA adduct levels in the leukocytes of 22-week old male C57BL/6J mice were in the range of 0.02-0.04 pmol adduct/mg DNA. Hepatic DNA adducts under the same conditions averaged 0.14 pmol/mg DNA while bladder DNA, adducts in these mice were as high as 13.4 pmol/mg DNA. These values correspond to 1 adduct in 10^8 nucleotides for leukocytes, 4 in 10^8 for liver, and 4 in 10^6 for bladder DNA.

Experiments currently in progress will examine the relationship of adduct levels in these tissues to changes in dosage and time of exposure.

Role of Oxidants in Hematopoietic Toxicity

*Lorraine E. Twerdok, Ph.D.**
Johns Hopkins University
School of Hygiene and Public Health
615 North Wolfe Street
Baltimore, Maryland 21205

** Now with: National Institutes of Standards and Technology, Building 245, Rm C214, Gaithersburg, Maryland 20899*

Program Area: *Occupational Cancers*
Grant Number: *5 R03 OH02632-02*
Start & End Dates: *09/30/88 – 09/29/90*
Funding Level: *$24,638 ($45,435 Cum)*

Importance to Occupational Safety and Health

Bone marrow is the target organ of many diverse chemicals, such as benzo[a]pyrene (BP) and benzene, that humans are exposed to environmentally and occupationally. This research is investigating target organ considerations in the role of oxidants in chemically-induced bone marrow toxicity. Oxidants within the bone marrow may participate in acute and/or chronic chemically-induced hemopoietic toxicity by either direct oxidant damage or indirect facilitation of chemical activation. Endogenous oxidant defense mechanisms within the bone marrow could be determinants in individual sensitivity to certain chemicals. Potentiation of chemical toxicity within bone marrow may also be an important factor for setting exposure levels. Therefore, knowledge of the mechanisms of bioactivation and inactivation within the target organ is important to predict risk and devise adequate protection and treatment regimes before and/or after exposure to chemical toxins and carcinogens.

Objectives

We are testing the hypothesis that oxidants generated by phagocytes in the bone marrow play a prominent role in some mechanisms of chemically-induced hemopoietic toxicity. It is the overall aim of this project to investigate the role of oxidants in hemopoietic toxicity by using benzo[a]pyrene-7,8-dihydrodiol (BP-diol) and hydroquinone (HQ) metabolites of BP and benzene, respectively, as model chemicals to study the

metabolism of xenobiotics by bone marrow derived from strains of mice with known susceptibility (DBA/2) and resistance (C57Bl/6) to orally administered BP.

Methodology

1. Chemilumigenic probing, superoxide anion production, and myeloperoxidase activity were used to compare oxidant generation between DBA/2- and C57Bl/6-derived bone marrow phagocytes.
2. Activation of BP-diol to a chemiluminescent species and an intermediate(s) which covalently binds to endogenous DNA was characterized and compared between the two strains of mice.
3. Target cell population(s) within the bone marrow will be identified using *in vitro* cell survival and colony forming unit (CFU) techniques.
4. Primary *in vitro* cultures of various bone marrow derived cells will be used to biochemically characterize putative protective enzymes in various cell populations of the bone marrow.

Significant Findings

DBA/2 mice, a strain with non-inducible P-450 systems, has been shown to be more susceptible than C57Bl/6 mice to the bone marrow toxic effects of both BP and benzene. We have compared the oxidant generation of neutrophilic cells isolated from femurs of male DBA/2 and C57Bl/6 mice. Oxidant generation of 12-o-tetradecanoyl-phorbol-13-acetate (TPA)-stimulated neutrophilic preparations was assessed by superoxide generation and oxidant-dependent chemiluminescence (CL) from luminol (myeloperoxidase-dependent) or lucigenin (superoxide-dependent). Cells from DBA/2 mice demonstrated increased oxidant generation as compared to those from C57Bl/6. Similarly, a two-fold enhancement of oxidant-dependent CL from BP-diol was observed with TPA-stimulated neutrophilic cells from DBA/2 mice as compared with cells from C57Bl/2 mice. This BP-diol-dependent CL was inhibited by the addition of azide or superoxide dismutase. Additionally, 25% greater covalent binding of BP-diol, the proximate carcinogenic metabolite of BP, to DNA was observed in the presence of TPA-stimulated neutrophils from DBA/2 mice (6.2 pmol/mg DNA) compared with cells from C57Bl/6 mice (4.7 pmol/mg DNA). These results suggest that the increased risk of DBA/2 mice for BP-induced leukemia may be related to their greater ability to generate oxidants which could participate in the activation of carcinogens as well as promote the development of bone marrow neoplasms.

Next, we examined if peroxidases could potentiate toxicity to stromal cells. HQ has been shown to be metabolically activated to an electrophile by both horseradish peroxidase (HRP) and myeloperoxidase (MPO), the peroxidase of myeloid cells. Stromal cells were selected as the target of toxicity since it has previously been demonstrated that these cells elaborate critical cytokines in the regulation of hematopoiesis. The toxicity of HQ to stromal cells was potentiated in the presence of H_2O_2 and either HRP or human MPO, such that nontoxic μM concentrations of HQ became toxic.

Activities of protective enzymes within the target organ, bone marrow, were also investigated. Quinone reductase (QR) is an important enzyme in protecting cells against the toxic effects of quinones and quinone metabolites which are common to both BP and benzene. Thus, whole bone marrow preparations from C57Bl/6 and DBA/2 mice were examined for their QR activity and a significant difference in QR activity was observed between these two strains of mice. Cells from C57Bl/6 mice had approximately 1.5-fold greater basal QR activity than those from DBA/2 mice. This difference in basal QR activity was also found in bone marrow primary stromal cells, cells which have been shown to be an important target of hydroquinone toxicity within the bone marrow. C57Bl/6-derived stroma had approximately twice the basal QR activity of DBA/2-derived stromal cells. This difference in basal QR activity between cells from C57Bl/6 and DBA/2 mice was reflected in relative susceptibilities to cellular toxicity induced by two quinone-generating compounds, tert-butylhydroquinone (tBHQ) and hydroquinone (HQ); DBA-derived cells, having lower QR activity, were more sensitive to both tBHQ- and HQ-induced toxicity. Recent studies have demonstrated that *in vitro* induction of QR protects hepatoma cells against quinone-induced toxicities. We have extended these observations and demonstrated that prior induction of QR by 1,2-dithiole-3-thione (DTT) also protects bone marrow stromal cells from both C57Bl/6 and DBA/2 mice against HQ-induced toxicity. QR activity and HQ-sensitivity was then evaluated in separated populations of bone marrow stromal cells, i.e., macrophages and fibroblasts. Again, the basal QR activity in each cell type directly correlated to HQ sensitivity. Stromal macrophages with lower basal QR activity were more sensitive to HQ. DTT was an effective chemoprotectant in these separated populations of stromal cells, as expected. Studies to assess *in vivo* DTT induction of QR within the bone marrow

compartment were completed in 1990 by the demonstration of induction of QR activity compartment following oral administration of DTT. Additionally, *in vivo* feeding of DTT protected bone marrow cells from *ex vivo* challenge to HQ.

Final studies with these project funds were aimed at evaluating functional rather than cytotoxic endpoints of hematotoxicity. Studies to date indicate that non-cytotoxic concentrations of HQ can have profound inhibitory effects on stromal cell ability to support and regulate hematopoiesis.

Publications

Twerdok LE, Rembish SJ, Trush MA: Studies with 1,2-Dithiole-3-thione as a Chemoprotector in Mouse Bone Marrow Stromal Cells. The Toxicologist 10:59, 1990

Trush MA, Twerdok LE, Esterline RL: Comparison of Oxidant-dependent Reactions by PMNs from Human, Rat, and Mouse: Implications for the Involvement of PMNs in Toxicological Reactions. Xenobiotica 20(9):925-32, 1990

Twerdok LE, Trush MA: Studies on Biochemical Determinants of Quinone-induced Toxicity in Primary Murine Bone Marrow Stromal Cells. In: Fourth International Symposium on Biological Reactive Intermediates: Molecular and Cellular Effects and Their Impact on Human Health, (eds. R Snyder, G Sipes), in press, 1990

Twerdok LE, Rembish SJ, Trush MA: An *In Vitro* Assessment of Determinants of Susceptibility of Mouse Bone Marrow Stromal Cells to Hydroquinone-induced Toxicity. In: Volume 7 - Alternative Methods in Toxicology Book Series, Seventh International CAAT Symposium, *In Vitro* Toxicology - Mechanisms and New Technology, Mary Ann Liebert, Inc., Publishers, New York, in press, 1990

Twerdok LE, Trush MA: Differences in Quinone Reductase Activity in Primary Bone Marrow Stromal Cells Derived from C57B1/6 and DBA/s Mice. Res Comm Chem Path and Pharmacol 67(3):375-386, 1989

Twerdok LE, Trush MA: Quinone Reductase (QR) as a Determinant of Stromal Cell Susceptibility to Hydroquinone (HQ). Toxicologist 9:289, 1989

Twerdok LE, Trush MA: 1,2-Dithiole-3-thione Protects Against Quinone-induced Toxicity to Murine Bone Marrow Stromal Cells. Proc American Association for Cancer Research 30:202, 1989

Activation of H-Ras Oncogene by N-Heterocyclic Aromatics

Susan F. Velazquez
University of Cincinnati
College of Medicine
Environmental Health
3223 Eden Avenue
Cincinnati, Ohio 45267-0056

Program Area: *Occupational Cancers*
Grant Number: *5 R03 OH02657-02*
Start & End Dates: *08/01/89 – 07/31/91*
Funding Level: *$13,007 ($29,007 Cum)*

Importance to Occupational Safety and Health

Polycyclic and N-heterocyclic aromatic hydrocarbons are ubiquitous pollutants being released into the environment from numerous sources such as coal tar, coke oven effluents, automobile exhaust, and cigarette smoke. Many of these compounds are known to be mutagenic and/or carcinogenic, but little is known about the mechanisms involved. This study is designed to investigate the ability of two N-heterocyclics, dibenz(a,j)acridine (DBA), and dibenzo(c,g)carbazole (DBC) to activate the H-ras oncogene in mouse skin carcinogenesis. The activation of this oncogene has been implicated as playing a role in the etiology of several experimental as well as human tumor types.

Objectives

The objective of this study is to determine whether mouse skin tumors initiated with DBA or DBC contain an activated H-ras oncogene. Mouse skin tumors initiated with the polycyclic aromatic compound 7,12-dimethylbenz(a)anthracene (DMBA) will be used as a positive control, as many different investigators have consistently shown DMBA to activate the H-ras gene. The nature and location of the activating mutations in the H-ras gene will also be determined.

Methodology

Since the outset of this proposal, there have been significant changes in the proposed

methodology in keeping with recent developments in the field of molecular biology. Initially, NIH3T3 transfection assays, Western blotting of the p21 protein, and Restriction Fragment Length Polymorphism (RFLP) analysis were proposed as the methods to study the activation of the H-ras gene. The research strategy has been modified to propose instead that regions of the mouse tumor DNA surrounding codons 12 and 61 (the two hot spots for mutational activation) will be amplified using the Polymerase Chain Reaction (PCR) technique, and subsequently, the DNA sequence will be determined.

Significant Findings

During the first year of the funding of this grant, the research focused on the NIH3T3 transfection assay. Tumor DNA was screened for its ability to transform the mouse fibroblast cell line resulting in the formation of foci. Positive results were obtained for transfections performed with DNA isolated from tumors induced by DMBA and DBA, but results from DBC samples could not be analyzed due to bacterial contamination. This technique is not currently being used. Initial work also involved looking at the electrophoretic mobility of the p21 protein encoded by the H-ras gene, as this can be used as an indicator of an amino acid substitution resulting from a DNA mutation. The preliminary results showed that there was a stronger ras signal seen in tumor samples than those from control mouse skins, and there was also an indication that p21 from DBA tumors migrated faster than control p21, suggesting a mutation in codon 61. RFLP analysis of codon 61 showed an A/T transition in DMBA tumor samples, but results were inconclusive for DBA. These techniques are no longer being pursued.

More recent efforts have centered on learning the techniques involved in PCR and DNA sequencing. The probes necessary for both of these techniques are being synthesized and the equipment for DNA sequencing has been obtained. A PCR unit is available through the Department of Molecular Biology at the University of Cincinnati. Preparation of DNA samples from mouse skin tumors is ongoing. This DNA will be amplified by PCR and sequenced for direct determination of mutations.

Explosion Hazards Related to Combustible Dusts

Charles W. Kauffman, Ph.D.
The University of Michigan
Department of Aerospace Engineering
2508 Patterson Drive
Ann Arbor, Michigan 48109-2140

Program Area: *Traumatic Injuries*
Grant Number: *5 R01 OH01122-08*
Start & End Dates: *01/01/81 – 03/29/92*
Funding Level: *$216,383 ($1,000,561 Cum)*

Importance to Occupational Safety and Health

The safety hazard resulting from finely divided combustible material has to some extent been recognized, although it would appear that these materials are not treated with the same concern as flammable liquids and gases. In the grain industry in fiscal 1990, there were 18 dust explosions, 11 injuries and 0 deaths. It is the grain and underground coal mining industries in which dust explosions are most prevalent. This situation is much improved from the late 1970's and early 1980's, in that in FY 1987 and FY 1990 there were no deaths as compared with the high for this decade of 11 in 1981. Additionally, the number of injuries has declined steadily from a decade high of 59, also in 1981. Data collected under the research effort supported by this grant has had an influence upon safety regulations for the grain industry put into effect by OSHA on March 31, 1988 and finally upheld by the U.S. Circuit Court.

Objectives

The purpose of this research project is to quantitatively characterize the explosion hazard represented by suspended and layered combustible dust. Using specially developed facilities, measurements are made which describe the fundamental aspects of dust combustion (laminar and turbulent burning velocities, denotation, velocity, reaction zone thickness, etc.) as a function of the parameters describing the initial conditions for the dust (chemical composition, size, shape, concentration, moisture content, premixedness, turbulence parameters including intensity and scale, etc.) Analytical efforts directed at the development of models which explain the observed phenomena are continuing.

Methodology

The suspended dust combustion studies are conducted in the Premixed Turbulent Combustion Bomb (PTCB) which is a spherical, one cubic meter jet-stirred reactor. The combustion process is initiated at the center of the well-characterized, uniform, turbulent dust cloud. During its propagation toward the vessel wall, appropriate measurements are made to characterize the burning process. The layered dust combustion studies are done in the extended Flame Acceleration Tube (FAT) which consists of seven continuous segments of 3000 psi working pressure steel tubing with a total length of 231 ft. and an inside diameter of one foot. It is closed at one end and open at the other. A controlled thickness and width dust layer is placed along the bottom of the tube, and it is then ignited by the combustion of a presuspended dust cloud (primary explosion) in the first twelve feet of the closed end. The history of the resulting combustion process as it accelerates toward the open end is monitored using regularly spaced appropriate instrumentation. In both of these facilities, the burning velocity and the post-combustion conditions are measured as a function of parameters characterizing the dust and pre-combustion thermodynamic conditions. Additionally, a horizontal and a vertical detonation tube are being used. In the vertical tube, which is 20 feet long and has a square internal cross section of 2.5 inches, it is possible to create a uniform, suspended dust-air mixture and to introduce at the top end a blast wave which may initiate a detonation. In the horizontal tube, which is 23 ft. long and has a 1.5 inch by 2.5 inch internal rectangular cross section, it is possible to deposit a uniform layer of dust along the bottom or narrow surface, for the length of the tube and then allow a blast wave to propagate into the tube which may initiate a detonation. Both facilities are instrumented to monitor the decay of the initiating wave or its transition into a steady detonation. One additional piece of equipment is used which allows the suspension of a dust particle in a controlled environment where it may be ignited and its subsequent combustion observed. Analytical work is being continued with regard to the layered dust combustion problem within the framework initially established by the U.S. Bureau of Mines, although this has now been significantly improved upon. For the suspended dust, much of the analysis depends upon that done by Bradley at Leeds for turbulent premixed gas flames. Modelling of dust detonations has been based upon the heterogeneous models originally developed at the University of Michigan with appropriate modifications. The modelling of

particulate combustion is similar to classic droplet combustion models and that done for coal particles.

Significant Findings

Using the particle on the fiber technique, the burning rate for individual cellulose (corn cob) particles has been established. Although this data applies to particles somewhat larger than desirable (>300 μm), it may be applied to nonspherical particles, and it is corrected for the nonsteady periods of ignition and extinction. The measured rate constant is in reasonable agreement with an analytical value. Detailed turbulence measurements made for both the standard 20 liter sphere and the 1 cubic meter Premixed Turbulent Combustion Bomb indicate that while the larger vessel produces much more uniform and steady turbulence conditions, it still does not yield the steady homogeneous turbulence field that is desirable. However imperfect though these results may be, they have caused the reexamination of the entire spectrum of results obtained from standard dust explosion test vessels. The layered dust experiments conducted in the Flame Acceleration Tube have quantified what has long been anticipated - that is possible to achieve a deflagration/detonation transition in a combustion process resulting from layered fuel. The observed combustion process produces overpressures as high as 30 atmospheres and travels at velocities as high as 1.5 km/sec. The industrial safety implications are significant in that in industrial facilities layered combustible dust is not uncommon, and that traditional suppression techniques, venting and fire bottles are ineffective. As a result of a long effort, there is presently some cause for optimism with regard to the development of an instrument which will measure the rate of the entrainment of the layered dust which provides the suspended fuel/air mixture whose combustion drives the detonation. The analytical work modelling this process continues to be successful. The accelerating flame produces a detached intensifying shock wave which eventually becomes strong enough to lead to the immediate post shock wave ignition of the dust particles which it is suspending, thereby producing the detonation wave and the associated retonation wave. These analytical results are, of course, quite dependent upon the values assumed for parameters such as the combustion time for the exothermic chemical reaction which in turn is determined by physical and chemical properties of the dust. As it was known from quite early work that suspended dust clouds can detonate and from the results which are noted here that layered dust deflagrations can transition to detonations, it would be expected that the direct initiation of the detonation of a dust layer should be possible with a blast wave. This condition has been difficult to achieve, occurring so far only with extremely high dust loadings, 11 kg/m^3, of cornstarch in pure oxygen with propagation velocities of 2 km/sec and overpressures of fifty atmospheres.

Publications

Sichel M: Numerical Modelling of Heterogenous Detonations. In Numerical Approaches to Combustion Modelling, (eds. ES Oran, J Boris), American Institute of Aeronautics and Astronautics, in press, 1989

Leisch SO, Kauffman SW, Sichel M: The Smoldering Combustion of Cellulosic and Starch Dusts. Proc of the International Conference in the Physical and Chemical Processes Occurring in a Burning Cigarette, RJ Reynolds Tobacco Co., Winston Salem, NC, 1987

Srinath SR, Kauffman CW, Nicholls JA, Sichel M: Secondary Dust Explosions. Industrial Dust Explosions, ASTM STP 958, Philadelphia, PA, 1987

Kauffman CW: Recent Dust Explosion Experiences in the U.S. Grain Industry. Industrial Dust Explosions, ASTM STP 958, Philadelphia, PA, 1987

An Epidemiologic Study of Injuries in Firefighters

Walter F. Stewart, Ph.D.
The Johns Hopkins University
615 N. Wolfe Street
Baltimore, Maryland 21205

Program Area: *Traumatic Injuries*
Grant Number: *5 R01 OH02254-02*
Start & End Dates: *06/01/87 - 10/31/89*
Funding Level: *$163,127 ($345,681 Cum)*

Importance to Occupational Safety and Health

This study identifies personal and environmental risk factors for injuries in firefighters, an occupational cohort at high risk of severe and fatal injuries. Future attempts to intervene to reduce work injuries in this occupation can be guided by knowing the highest risk groups and situations, as

well as the most common events associated with injury.

Objectives

The overall purpose is to determine how to reduce the risk of occupational injuries among firefighters by improving our understanding of the contributing factors. One objective is to describe the occurrence of injuries among Baltimore firefighters. Another objective is to determine more specific risk factors for disabling injuries received on the fireground. Variables include: (1) personal attributes of firefighters, (2) work patterns, and (3) situational and environmental factors.

Methodology

This epidemiologic study is a case-control study of firefighters injured on the fireground during a one-year period in Baltimore City and Baltimore County. Sources of data are interviews, injury reports, and fire incident reports.

Significant Findings

Personal risk factors: Age is an important risk factor for injury in firefighters, even after controlling for environmental hazards. No association was observed between alcohol consumption and risk of injury. Environmental risk factors: Many environmental hazards contributed significantly to injury risk, including size of fire, noise level, degree of smoke, and stage of fire at time of arrival on the fireground. Task risk factors: Extinguishment was the firefighting task associated with highest risk of injury, followed by overhaul and ventilation.

Publications

Braver ER, Stewart WF, Baker SP, Celentano DD, Edwards CA, Howard SR: Injuries in Firefighters: Do We Really Need a Case-Control Study? Abstract published in the Proceedings of the 116th Annual Meeting of the American Public Health Association, Boston, Massachusetts, November 13-16, 1988

Reduction of Occupational Injury Deaths in Rural Colorado

Carol J. Garrett, Ph.D.
Colorado Department of Health
Health Statistics Section
Division of Health Statistics and Vital Records
4210 East 11th Avenue
Denver, Colorado 80220-3716

Program Area: *Traumatic Injuries*
Grant Number: *5 R01 OH02601-03*
Start & End Dates: *09/30/88 – 09/29/91*
Funding Level: *$173,274 ($469,792 Cum)*

Importance to Occupational Safety and Health

Half of the occupational injuries in Colorado that result in death occur in rural areas where only 20% of the workforce resides. Thus, rural occupational injury deaths constitute a major public health problem in Colorado, and if this pattern holds in other states with rural areas, it represents a public health problem nationally.

Major risk factors contributing to the urban/rural difference in occupational injury mortality will be identified in this study. The goal of reducing rural deaths can be attained only by identifying and addressing those risk factors that are preventable.

Objectives

Through substantial augmentation of the Colorado Population-based Occupational Injury and Fatality Surveillance System, risk factors plausibly responsible for urban/rural differences in Colorado occupational injury mortality will be investigated. Factors will be quantified and classified according to pre-event, event, and post-event phases, and include company size, injury severity, circumstances of injury, EMS responsiveness, trauma care effectiveness, and alcohol association. Results of analysis and experience gained from case investigations will be used to identify and prioritize intervention strategies to reduce rural occupational injury deaths.

Methodology

Occupational injury deaths are ascertained primarily by linkage of workers' compensation claims (WC), OSHA case reports, and death

certificates (DC). Additionally, motor vehicle traffic accident reports are linked for occupational traffic deaths. Injury rates by industry and region are calculated based on workforce estimates from the Bureau of Economic Analysis' (BEA) Regional Economic Information System.

Company size information is obtained from several sources: OSHA 170 computerized summaries, WC employer's first report of injury, state employment statistics (ES-202 files) and, as needed, direct query of employers. Workforce by company size (denominators for rates by company size) are estimated by applying Small Business Administration estimates of the distribution of the workforce by company size to BEA figures.

Injury severity is determined by assigning Injury Severity Scores (ISS) using all available information on deaths (coroner's reports, autopsy reports, and emergency room and hospital records) and on seriously injured survivors (hospital summaries and discharge diagnoses). Occupational injury hospitalizations will be identified from method of payment (workers' compensation) on the statewide uniform hospital discharge data set from the Colorado Hospital Association. The serious, nonfatal, hospitalized injuries will be identified initially by computing ISS scores from discharge diagnoses via software developed at The Johns Hopkins University. Analysis will include calculation of preventable death rates by region and, by incorporating survivors with high ISS scores, calculation of trauma care effectiveness.

Secondary sources utilized for determining circumstances of injury for fatalities (prior to April 1989 when active case investigations began) include death certificate, WC employer's first report, OSHA 170 computerized summaries, and coroner's reports.

Active case investigation of civilian nontransportation unintentional injury deaths not within the jurisdiction of OSHA and MSHA constitute a major intervention strategy. The active case investigations are conducted using the Fatal Accident Circumstances Epidemiology (FACE) protocol developed by NIOSH. Cooperation and collaboration with industry and labor groups, as well as with OSHA and MSHA, is being fostered.

Evaluation of EMS responsiveness by region will rely primarily on survey data from the EMS Division at the Colorado Department of Health and their assistance in collecting copies of EMS trip reports, since anticipated implementation of a statewide, automated trip report system has been delayed.

Significant Findings

Firm size is an independent risk factor for occupational injury fatality. For the period 1982-87, the risk for workers in firms with 500+ employees was 1.7 deaths per 100,000 workers, while that for employees in firms of <20, 20-99, and 100-499 was 11.0, 9.0, and 11.5/100,000, respectively. Regional location plays an independent and dominant role when firm size is considered. For workers in firms with fewer than 500 employees compared to workers for firms of 500+, the risk of occupational injury fatality is 7.6 times greater in the Denver region and 4.1 times greater in the rural region.

Injury severity as determined by assigning Injury Severity Scores (ISS) to 85% of the eligible deaths for 1986-88 emerges as a major factor explaining the rural/urban difference in mortality. Of all rural deaths, 65% are nonsalvageable (ISS 50+), whereas only 38% of the Denver CMSA deaths are non-salvageable. Using the employed population for calculating rates, the rural/urban rate ratio for nonsalvageable deaths is 6.4 (4.5-9.2) while the salvageable death rate ratio is only 1.9 (1.2-3.0). Thus, the greatest opportunity/challenge is to reduce nonsalvageable deaths with a focus on primary prevention involving pre-event and event factors. It has been possible to assign ISS to hospitalized, work-related injury survivors during 1986-88. Utilizing ISS of 16-49 as the potentially salvageable range for both deaths and survivors over the three-year period, the statewide trauma care efficacy rate is 74.5%. This overall efficacy compares quite favorably to that of the Multiple Trauma Outcome Study and suggests that trauma care efficacy is quite good.

Circumstances of injury have been studied by active case investigation of all 41 non-transportation unintentional injury deaths occurring after April 1989. The industrial hygienist for the project has participated in 23 (56%). In 8 (20%) he conducted investigations alone since they were outside OSHA and MSHA jurisdiction. Joint investigations using the FACE protocol have been quite successful. Investigation results to date point to violations of known standards and practices. It is the rare incident that suggests the outcome would have been altered by immediate trauma care.

Publications

Marine WM, Garrett CJ, Keefer S, Vancil R, Hoffman R, McKenzie L: Occupational Injury Deaths in Colorado 1982-87. Colorado Department of Health, 1990

Marine WM, Keefer S, Vancil R, Garrett CJ, Hoffman R, Metcalf L, Moser K: Rural/Urban Differences in Injury Severity Scores of Occupational Injury Deaths. APHA, 1990 (Abstract)

Keefer S, Marine WM, McKenzie L, Vancil R, Garrett CJ: Industry-Specific Profile of Fatal Occupational Injuries from Six Years of Surveillance. APHA, 1990 (Abstract)

Marine WM, Keefer S, Vancil R, Garrett CJ: Statewide DUI Enforcement and Work-Related MVA Traffic Fatalities in Colorado, 1982-1987. APHA, 1990 (Abstract)

The Health Hazards of Child Labor

Philip J. Landrigan, M.D.
Mount Sinai School of Medicine
Department of Community Medicine, Box 1057
New York, New York 10029

Program Area: *Traumatic Injuries*
Grant Number: *5 R01 OH02717-02*
Start & End Dates: *12/01/89 - 11/30/91*
Funding Level: *$56,846 ($56,846 Cum)*

Importance to Occupational Safety and Health

In this study, rates of work-related injury for children under age 18 in New York State are being computed by age, sex, occupation, and industry. Trends are assessed for the years 1980-1987. Descriptive analyses of occupational injuries in working children are being undertaken within each age group, occupation, and industry, and these are related to extent of disability. Detailed information on circumstances surrounding occupational injury in children has been sparse despite the existence of more than 4,000,000 working children. Increasing this information would improve possibilities for prevention.

Objectives

With specific epidemiologic information on injuries in working children, better preventive measures can be designed and targeted to high risk situations. The overall purpose is to lessen the significant toll of occupational injuries children are incurring by describing the rates of such injuries and the circumstances surrounding them. Elucidating patterns of injury by age, sex, industry, occupation, body part, and extent of disability will make it possible to improve education, legislation, and workplace safeguards to reduce the number of pediatric occupational injuries.

Methodology

This is a population-based descriptive epidemiologic study. Workers compensation tapes for awards to New York State children under age 18 for the years 1980-1987 provide numerator data for rates. Denominator data for rates comes from the Annual Demographic File, a March telephone supplement to the Current Population Survey. Hospital discharge tapes and surveys of working children provide additional data sources.

Significant Findings

From 1980 - 1987, a total of 10,047 children under the age of 18 received compensation for work-related injuries form the New York State Workers' Compensation Board. The majority of these children were male (75%) and were 16 and 17 years old (86%). On average, 1,256 children were compensated for work-related injuries per year. While relatively few children age 15 and under were injured at work, the younger children accounted for an important segment of those with permanent disabilities. Rates and further descriptive factors will be discussed in forthcoming papers.

Publications

Pollack S, McConnell R, Galleli M, Schmidt J, Obregon R, Landrigan P: Pesticide Exposure and Working Conditions Among Migrant Farmworker Children in Western New York State. Abstract published in the Proc of the American Public Health Association Annual Meeting, New York, October 4, 1990

Pollack S, Belville R, McConnell R, Landrigan PJ: Work-Related Injury to Adolescents in New York City. Abstract published in the Proc of the American Public Health Association Annual Meeting, New York, October 4, 1990

Pollack S, Landrigan P, McConnell R, Belville R, Solomon J, Wu X: Epidemiologic Studies on the Health Hazards of Child Labor. Abstract published in the Proc of the 23rd International Congress on Occupational Health, Montreal, Canada, September 28, 1990

Landrigan PJ, Pollack S, Belville R, McConnell R: Epidemiologic Studies on the Health Hazards of Child Labor. Abstract published in the Proc of the Annual Meeting of the American Pediatric Society/Society for Pediatric Research, Anaheim, California, May 10, 1990

Pollack SH, Rubenstein H, Landrigan PJ: Child Labor. Maxcy-Rosenau Public Health and Preventive Medicine, 13 edition, in press, 1990

Pollack SH, Landrigan PJ, Mallino DL: The Health Hazards of Agricultural Child Labor. Migrant Health Clinical Supplement May/June, 1990

Pollack SH, Landrigan PJ: Child Labor in 1990: Prevalence and Health Hazards. Annu. Rev. Public Health 11:359-375, 1990

Case-Control Study of Sawmill Injuries in Maine

Laura Punnett, Sc.D.
University of Lowell
Department of Work Environment
One University Avenue
Lowell, Massachusetts 01854-2881

Program Area: *Traumatic Injuries*
Grant Number: *1 R01 OH02741-01*
Start & End Dates: *06/01/90 – 05/31/93*
Funding Level: *$54,653 ($54,653 Cum)*

Importance to Occupational Safety and Health

Lumber and wood products processing (SIC 24) is the second largest industry in Maine, with an annual average employment of approximately 13,500 workers, accounting for about 13% of the manufacturing workforce. In 1987, the incidence of OSHA recordable injuries and illnesses in sawing and related mills, excluding logging (SIC 242-249), was 29.1 cases per 100 workers, more than twice the average statewide rate. Preliminary analyses of cases recorded on the OSHA Form 200, as well as Workers' Compensation First Reports of Injury, suggested that about two-thirds of the lost-time injuries were acute traumatic incidents and one-third were musculoskeletal disorders.

A number of specific safety and ergonomic hazards have been identified in Maine sawmills. These include unguarded platforms, stairways, and floor openings; dangerous and improperly guarded equipment; manual materials handling of logs and other heavy items; unshielded hot surfaces; excessive noise; and carbon monoxide from power equipment exhaust. Although these hazards are virtually ubiquitous, the conditions under which they actually result in energy transfer and injury have not been well defined by epidemiologic analysis. The sparse literature on injuries in this industry is primarily descriptive, with little insight into causal factors that could be preventable, particularly by means of ergonomic or safety engineering controls.

Objectives

The primary objective of the proposed research project is to identify the wood product processing activities, equipment, and working conditions that are associated with increased risk or severity of acute traumatic events and musculoskeletal injuries, and to identify etiologic associations and the opportunity for preventive interventions.

Methodology

A case-control study is being conducted of risk factors in the work environment for occupational injury in the Maine wood products industry (SIC 242-249). A population-based, case-control study design will be employed in which cases will be identified from employers' First Reports of Injury filed with the State Workers' Compensation Commission and collected for the U.S. Department of Labor Supplementary Data System. Controls will be selected from employee lists provided by participating employers or from membership lists provided by participating union locals.

All subjects will be interviewed to obtain information on demographics, anthropometry, work history, and medical history. The interview will also obtain information on production tasks, characteristics of the equipment, tools and product, and other features of the work environment. For cases, this information will be obtained regarding the specific activities performed on a typical work day and at the time of the injury. Controls will be asked about their work activities on a typical work day and on the last day worked on the same day of the week as the index injury. Exposure items will include specific ergonomic features and general working conditions, including tool weight, noise, thermal environment, illumination, work pace, heavy lifting, machine pacing, piece rate wages, overtime, shift work, and volume of production output. Subjects will also be asked about the presence and activities of any workplace health and safety programs, such as worker training or labor-management committees.

Supplementary exposure data will be collected by a variety of means to attempt to validate the interview information. Where possible, the plant mechanics in participating mills will be contacted after the interviews for additional specific information on equipment, tools, and machinery. For a sample of study respondents, the investigators will visit the plants in order to evaluate working conditions, using a standardized safety and ergonomic job analysis methodology modified to adapt it to this particular industry. All participating mills have been requested to provide any environmental data that might have been available for noise, heat, dust levels, etc., through in-house monitoring or OSHA inspections.

Exposure odds ratios will be computed to estimate the risk associated with specific factors for each type of injury and body part. Some features of the work environment are hypothesized to affect the risk of injury in a manner that is not highly specific to the type of injury. Factors such as piece work vs. hourly wage, shift worked, work pace and production output, noise intensity, heat and humidity, and work on a temporary vs. usual job assignment may be associated with a general increase in injury rates because they cause generalized fatigue, difficulty in safely maintaining the required work pace, or unfamiliarity with safe operating procedures.

In addition, a series of specific hypotheses will be examined regarding risk factors for different types of injuries. For example, strains and sprains of the back will be studied with respect to weight of loads in manual material handling and the trunk postures used to operate tools or machinery. Acute injuries (cuts, lacerations, contusions, etc.) of the upper extremity will be analyzed with respect to use and characteristics of gloves, non-neutral upper extremity postures, and the length of the exposed blade or cutting surface. Slips and falls will be studied in relation to heat and humidity, workload intensity, respirator use, weight of loads handled, and condition of the floor surface.

Significant Findings

A standardized questionnaire was developed based on discussions with sawmill workers and health and safety officers. It has been pre-tested and revised several times following interviews with injured sawmill workers identified by First Reports of Injury.

A renewed effort to recruit additional sawmills and wood processing plants has significantly increased the number of employers participating in the study. At present, a total of 14 facilities, with an active workforce of about 700 employees, and three union locals with about 800 members represent the study base from which controls may be selected. (Additional participants may still be added in the next few months.)

Probabilities of Job-Related Deaths and Disabilities

J. Paul Leigh, Ph.D.
San Jose State University
Department of Economics
One Washington Square
San Jose, California 95192-0114

Program Area: *Traumatic Injuries*
Grant Number: *1 R01 OH02760-01*
Start & End Dates: *09/01/90 – 08/31/91*
Funding Level: *$62,043 ($62,043 Cum)*

Importance to Occupational Safety and Health

While the Bureau of Labor Statistics regularly publishes lists of industries according to illness and injury rates, few lists of jobs are available which rank occupations by mortality and/or disability rates. This is unfortunate for two reasons. First, OSHA resources need to be targeted to not only high risk industries but high risk occupations as well. Second, the public would benefit from having greater information on job hazards just as they benefit from nutrition labels on packaged and canned food. Future laws may require that job hazards and mortality statistics be included on all job application forms. (Leigh, Occupational Hazards, in press)

Objectives

The proposed research will generate 18 tables of job-related injury probabilities within roughly 350 occupations as follows:

(1) Death rates and (2) permanent disability rates for men and women, 1978-1985.
(3) Death rates and (4) permanent disability rates for men and women, 1978-1981.
(5) Death rates and (6) permanent disability rates for men and women, 1983-1985.

Tables 7-12 will be similar to tables 1-6 but will be restricted to women. Tables 13-18 will be similar to tables 1-6 but will be restricted to men.

The proposed study will analyze each of these 18 tables and will compare women with men; 1978-1981 with 1983-1985; deaths with permanent disabilities; and deaths with rankings of occupations by blood pressure. (Ranking occupations based upon the blood pressures of incumbents, in press for JOM)

Methodology

The U.S. Bureau of Labor Statistics has been collecting information on deaths and disabilities on people filing claims and being awarded benefits from Worker's Compensation Boards in roughly 32 states since 1976. The data are stored in the Supplemental Data System (SDS). Information is available (1) on the age, sex, and 3-digit U.S. Census occupation for each person; (2) on the nature of the injury or illness; and (3) on whether the injury or illness resulted in death or permanent disability. To date, these data have not been widely analyzed. This is especially unfortunate for injuries given the little research attention to injuries within occupations as opposed to industries. (Injury in America, p. 42)

The proposed research will build on a prior study which used some of the early SDS data (Leigh, J Occup Med 29:510, 1987). The prior study used only fatality data from 11 states during 1977 to 1980 to construct annual probabilities of job-related deaths within 347 occupations. Probabilities were calculated by taking the ratio of fatalities to estimated employment within each occupation for each state and each year. The proposed research will differ from the prior 1987 study by (1) considering permanent disabilities; (2) considering the most recent years available: 1981, 1983, 1985; and (3) separating male from female probabilities of job-related deaths and disabilities.

Significant Findings

None to date.

Evaluation of a Database for Occupational Injury Surveillance

Gary Sorock, Ph.D.
New Jersey State Department of Health
Division of Occupational
and Environmental Health
CN 360
Trenton, New Jersey 08625-0360

Program Area: *Traumatic Injuries*
Grant Number: *5 R03 OH02579-02*
Start & End Dates: *09/15/88 - 02/28/91*
Funding Level: *$19,225 ($37,236 Cum)*

Importance to Occupational Safety and Health

Severe occupational injury is among the ten categories of leading work-related diseases and injuries identified by NIOSH for in-depth study and prevention. The New Jersey State Department of Health is evaluating the usefulness of its statewide hospital discharge database ("UB-82" database) for surveillance and epidemiologic study of severe, non-fatal, occupational injuries. The injuries, resulting in hospitalization, are finger amputation, thumb amputation, crush injury of the lower limb, toxic effects of poisoning by metals, and eyeburns. Hospital discharge data are an attractive new source of injury surveillance information.

Accurate surveillance of severe occupational injuries will provide us with a baseline estimate of the statewide incidence of these five types of work-related injuries which required hospitalization. Epidemiologic data gathered by personal interviews in this study will help target high-risk industries, occupations, machinery, and work behaviors for future intervention activities to prevent these injuries. It is anticipated that the knowledge gained from this study will indicate which data from the hospital discharge database most accurately reflect the work-related injury experiences of persons hospitalized in New Jersey in 1985 and 1986. This information, together with our epidemiologic data, should be of use to other state health departments as they plan their use of hospital discharge data for injury surveillance and prevention.

Objectives

The objectives of this study are to:

1. Collect information on individuals identified by the UB-82 database who had one of five types of injuries: finger amputation, thumb amputation, crush injury of the lower limb, chemical poisoning, and eye burns.
2. Determine by interview the proportion of injury cases that are work-related.
3. Describe work-related injuries by type of job held at time of injury.
4. Describe and compare characteristics of cases paid for by workers compensation with those paid by other sources of each injury type.
5. Determine the types of injury and the characteristics of cases for which the UB-82 database would provide the best surveillance.
6. Determine whether external cause of injury codes added to the UB-82 data would provide a significant increase in the quality and usefulness of the UB-82 data for injury surveillance.

Methodology

The methods used in this study are: (1) to utilize the UB-82 database to create a file containing records with a primary diagnosis of one of five serious, non-fatal injuries; (2) to request New Jersey hospitals to provide patient identifying information and the attending physician's name so that individual patients can be contacted by letter to participate in the study; (3) to interview patients by phone regarding the injury incident and its work-relatedness and to ask permission to gain access to medical records; (4) to corroborate the interview data with medical record information and worker's compensation data; and (5) to analyze data to determine whether UB-82 data are useful for surveillance of occupational injuries, and whether ICD-E codes would increase the usefulness of hospital data for surveillance purposes.

Significant Findings

The interview phase of this study is now complete. We attempted to contact 809 persons discharged from New Jersey hospitals in 1985 and 1986 with one of five selected injuries. Of 809 potential subjects who were sent letters, 302 (37%) were interviewed by telephone. We were unable to reach 507 (63%) potential subjects. Two-hundred sixty-five persons moved (33%), 143 refused to participated (18%), 73 had unpublished telephone numbers (9%), and 26 were unable to be reached for other reasons (3%).

One person interviewed did not identify the type of injury received. Eliminating this non-response from the total number of interviews, the numbers and percents of 301 interviews by injury type were: finger amputation (171, 57%), thumb amputation (69, 23%), crush injury of the lower limb (48, 16%), chemical poisoning due to heavy metal (5, 1%), and eye burns (8, 3%). The numbers and percents of the completed interviews by injury type that were work-related were: finger amputation (100, 58%), thumb amputation (34, 49%), crush injury of the lower limb (33, 69%), chemical poisoning (3, 60%), and eye burns (4, 50%).

The interview data from 302 completed interviews were examined for the amount of agreement between work-relatedness of injury by self-report and the presence of workers' compensation in the primary payor field on the UB-82 database. The percent agreement was 89%, and the agreement beyond chance (Kappa) was 0.78 which is interpreted as excellent agreement. The 95% confidence interval for this estimate of Kappa is (0.67-0.89). This result suggests that workers' compensation payment on the UB-82 database may be a good to excellent proxy indicator of work-relatedness of these injuries.

Through November 1990, 119 of 302 (39%) interviewed subjects returned signed medical record release authorization forms. To date, 115 (97%) of the 119 medical records have been obtained, abstracted and coded, when possible, using E-codes. These data will be used to verify the interview information and assess the utility of routinely adding E-codes to medical records.

A final report is currently in progress.

The Effect of Localized Fatigue on Postural Stability

Richard J. Wickstrom
University of Cincinnati
College of Medicine
Environmental Health
3223 Eden Avenue
Cincinnati, Ohio 45267-0056

Program Area: *Traumatic Injuries*
Grant Number: *5 R03 OH02653-02*
Start & End Dates: *04/01/89 - 03/31/91*
Funding Level: *$22,690 ($43,365 Cum)*

Importance to Occupational Safety and Health

Slips and falls at work account for 14-23% of all lost-time work injuries, and a mortality rate of 4.6

deaths per year per 100,000 workers. Injuries from slips and falls are frequently serious, with an incidence rate rising in direct proportion to increasing age. Tiredness or fatigue has been cited as an important risk factor for slips and falls in the high risk construction and manufacturing industries, because the most common activities performed prior to falls from elevations are static postural efforts and manual materials handling. Although uncontrolled high energy expenditures during dynamic work may eventually lead to fatigue, static work activities can produce localized muscle fatigue and discomfort after short duration activities. Given the significant economic costs and chronic disability associated with falls, more emphasis must be given to identifying and controlling those factors responsible for falls in high risk industries. To date, there are no existing guidelines that consider the criteria of postural stability during the evaluation and control of fatigue during static work and manual lifting.

Objectives

The purpose of this two-year study is to evaluate the effect of localized fatigue from static muscle loading and manual lifting activities on standing steadiness. The study will also determine if ratings of perceived exertion and discomfort can accurately predict the effect of a given work activity on postural stability. The study's broad, long-term objective will be to suggest practical ergonomic guidelines for the evaluation and control of static work activities and manual lifting based on their potential impact on human postural stability. The specific objectives for year one of the project are:

1. To determine the effect of sustaining stooped versus squat versus erect standing posture for different time periods on fatigue parameters of standing steadiness, heart rate, perceived exertion, and discomfort.
2. To determine the effect of induced fatigue of individual postural muscle groups (trunk extensors, trunk flexors, knee extensors, knee flexors, ankle dorsiflexors, and ankle plantar flexors) on standing steadiness.

The specific objectives for year two of the project are:

1. To determine the effect of repetitively lifting the NIOSH Action Limit, using the stooped versus partial squat versus erect posture, on fatigue parameters of standing steadiness, heart rate, and perceived exertion.
2. To determine the efficacy of using the present NIOSH Work Practices Guide for Manual Lifting to reduce the risk of postural instability due to localized fatigue from manual lifting in different postures.

Methodology

A total of 36 healthy males, aged 21-35 years, will be studied during each experiment. Males were chosen because of the stressful nature of the lifting task. Fatigue estimates of standing steadiness, heart rate, ratings of perceived exertion, and ratings of discomfort will be the dependent variables to be collected prior to and following each condition for all experiments. During Experiment One, subjects will be exposed to fatigue of six postural muscle groups at two levels of loading. The level of loading on each individual postural muscle group (plantar flexors, dorsiflexor, knee flexors, knee extensors, trunk/hip flexors, and trunk/hip extensors) will equal 30% or 70% of the muscle group's maximum static strength, maintained as long as possible by the subject. During Experiment Two, subjects will be exposed to four doses of fatigue in three different work postures. The doses of fatigue will be 25%, 50%, 75%, and 100% of the maximum holding time for manipulating small pegs in the stooped or crouched postures. The highest maximum holding time for the stooped or crouched posture will be used to set the holding times for the comparison of erect standing posture. During Experiment Three, subjects will be exposed to two frequencies of lifting (2 & 6 lifts/minute) the NIOSH Action Limit in the same three work postures used for Experiment Two. The basic design for each of the three experiments will be a fractional factorial Latin-square design, to allow assessment and balancing of any systematic or additive effects associated with the order of testing, related practice, fatigue, transfer of training, etc.

A multi-axis biomechanics force platform, in conjunction with a customized pattern recognition algorithm, will be used to quantify standing steadiness during quiet standing with eyes closed. Additionally, objective measures of heart rate and the worker's perceived stress will be used to quantify the response of the body to the conditions of Experiments 1-3. Borg's 10 point rating of perceived exertion and Sauter's 4 point rating of discomfort were modified slightly by the investigator to improve the clarity and utility of these scales for a variety of clinical, field, and research applications.

Significant Findings

Sufficient data have not been collected and analyzed to permit disclosure of significant findings at this time.

Analysis of Seafood Processing Injuries/Illnesses

Bernice W. Carmon, R.N., M.P.H.
University of Alaska
College of Nursing and Health Sciences
3211 Providence Drive
Anchorage, Alaska 99508

Program Area: *Traumatic Injuries*
Grant Number: *1 R03 OH02656-01*
Start & End Dates: *02/01/90 - 01/31/91*
Funding Level: *$19,159 ($19,159 Cum)*

Importance to Occupational Safety and Health

The goal of this study is to improve understanding of the factors and emerging trends associated with occupational injuries in the seafood processing industry in Alaska. Information generated by this study will provide a basis for planning preventive strategies to reduce the incidence of work-related injuries among seafood workers.

Objectives

The objectives of the study are:

1. Develop demographic and occupational profile of workers injured in the seafood processing industry in Alaska over the three-year period from 1985-1987.
2. Identify high-risk occupations within the seafood processing industry and the characteristics of the injuries most frequently sustained by workers in these occupations.
3. Derive hypotheses that can be used to direct future research on injuries in the seafood processing industry.

Methodology

This is a descriptive study. Pre-coded Worker's Compensation data extracted from cases of occupational injuries/illnesses filed by seafood processing workers in Alaska are being re-analyzed using bivariate and multivariate statistical tests.

Significant Findings

Interim results of the study indicate that during the three year period from 1985 through 1987, a total of 2707 Worker's Compensation claims were filed by workers employed in the seafood processing industry in Alaska. Ninety-two percent of the claims involved injuries. Seventy-five percent of all injuries occurred within the first 3 months of employment. The predominant nature of the injuries were sprains and strains (35%), contusions and bruises (17%), cuts and lacerations (12%) and fractures (8%). Body parts most frequently injured were wrist hand and fingers (26%) and the trunk (30%). Most injuries clustered among workers employed as pack/fill machine operators and miscellaneous hand work operators. These two occupational groups accounted for 72% of all reported injuries. Further analysis of these groups is in progress.

Incidence of Work-Related Injury

Marjorie E. Nelson, M.D.
Ohio University
College of Osteopathic Medicine
Department of Family Medicine
346 Grosvenor Hall
Athens, Ohio 45701

Program Area: *Traumatic Injuries*
Grant Number: *7 R03 OH02659-02*
Start & End Dates: *06/01/89 - 05/31/91*
Funding Level: *$21,300 ($42,691 Cum)*

Importance to Occupational Safety and Health

There exists no comprehensive, widely accepted source of information on the incidence of work-related injury in the United States. This study attempts to make an independent estimate of this incidence using a medically-based system (emergency department visits) and an employment-based system (lost-time claims to Workers' Compensation). Merging incidence data from these two systems for one community will allow an independent estimate which can be compared to Bureau of Labor Statistics (BLS) estimates and help determine the validity of these BLS estimates.

Objectives

The principal aim of the project is to make estimates of the frequency of occurrence of workplace injuries that result in either an emergency room (ER) visit or a lost-time claim coded by the Ohio Industrial Commission, or both, for Athens County, Ohio during the years 1982-86. A secondary aim is to compare this incidence estimate to the expected number obtained by applying national BLS industry-specific incidence rates to the number of persons employed in Athens County by industry.

Methodology

Primary data sources are data tapes containing (1) National Electronic Injury Surveillance System (NEISS) data on injured persons treated at the major hospital in Athens and (2) lost-time claims to the Workers' Compensation System for persons employed in Athens County. Both datasets cover the period 1982-86 inclusive. They are being merged on social security number, where possible, and on date of injury, age, sex, and type and location of injury to produce an unduplicated count of injured workers. In addition, a sample of work-related emergency room visits at the other hospital in the county has been abstracted to allow estimates of work-related injuries treated at that hospital, and a random sample of work-related ER records from the principal hospital has been abstracted to estimate completeness of the NEISS dataset.

Significant Findings

The NEISS and workers' compensation datasets from 1982-86 have been reviewed and matches identified by application of an algorithm developed to look at social security number, date of injury, age, sex, and type and location of injury. The total of ER visits plus workers' compensation claims is approximately 1,250 per year. This number was derived after accounting for duplicate records appearing in both datasets, and after correcting for the number of occupational injuries seen in the ER but not entered into the NEISS dataset.

Further definition of the employed population and the employers in the county is almost complete. Significantly:

1. Ninety-two percent of the 52 major employers in the county during 1982-86 have been contacted. Six of the employers contacted, employing about 14% of the work force in the set of major employers, are self-insured for workers' compensation and file lost-time claims only after 7 days of lost work time. These include a mining operation and a large shoe manufacturing company.
2. The largest employer in the county, Ohio University, has physicians on the premises who treated 226 work-related injuries during 1982-86. These encounters were not included in the NEISS dataset and some of them did not result in lost work time and were not included in the workers' compensation dataset. A shoe manufacturing company, previously thought to have an arrangement with a local physician for treatment of injuries occurring on the job, in fact did not have such an arrangement during the study years. One mold and machine company sends employees with eye injuries directly to the offices of local ophthalmologists, but uses the hospital emergency room for other injuries.
3. An additional 250 employees of a mining operation have been identified who are not residents of the county but would be expected to receive injury-related care at local facilities.

Subsequent work will include completing employee/employer profiles and analyzing and comparing the match data to see how each portrays work-related injuries in Athens County. The match data will also be compared to BLS estimates.

Stress Effects of Human-Computer Interactions

Henry H. Emurian, Ph.D.
The University of Maryland
Baltimore Campus of Arts, Sciences, and Technology
Baltimore, Maryland 21228

Program Area: *Cardiovascular Diseases*
Grant Number: *1 R01 OH02614-01A1*
Start & End Dates: *09/01/89 - 08/31/91*
Funding Level: *$26,630 ($26,630 Cum)*

Importance to Occupational Safety and Health

Exaggerated blood pressure responses to brief and repeated behavioral challenges have been implicated as a potential component in the complex etiology of coronary heart disease (CHD). Typical human-computer interactions undertaken by data entry and retrieval clerks within the workplace may occasion such cardiovascular hyperresponsivity and, accordingly, may pose risk for the development of CHD. Identification of such a risk factor in the workplace is the first step toward intervention or prevention. Differential cardiovascular responsivity according to personality type may allow identification of a group of individuals, through personality testing and screening, at comparatively high risk for CHD. Angry Type A users of computer systems in the workplace, at least, may require warnings regarding the potential adverse health consequences of their work, if not periodic assessment of cardiovascular functioning and mood.

Objectives

This research aims to compare blood pressure and heart rate responses exhibited by Type A and Type B normal male volunteers in relationship to database query task performance and operating system throughput variability that are frequently encountered during a video display terminal (VDT) operator's work. Masseter (jaw) and corrugator supercilii (brow) EMG responses will also be obtained as real-time "microaggressive" responses emitted by operators during human-computer interactions. It is hypothesized that angry Type A users, in comparison to Type B, will show elevated cardiovascular and EMG responses during variable throughput delays between the entrance of a query command and the final display of data.

Methodology

A treatments by levels experimental design will be used. Subjects will be typed by the Videotaped Structured Interview. Fifteen Type A subjects will be assigned to either a constant or variable throughput condition, as will 15 Type B subjects. Subjects will operate a synthetic data retrieval task while blood pressure, heart rate, masseter, and corrugator supercilii responses are assessed. Following a 60-minute resting baseline session not including task performance, a performance session will consist of 30 minutes of task performance under each of 2 throughput conditions, counterbalanced across subjects. Initial baseline means will be used as covariates for ANCOVAs with means for all baseline and task components of the performance session.

Significant Findings

In a preliminary study, ten untyped normal males solved 50 database queries consecutively presented on a video display terminal (VDT). Each query required a solution within 45 seconds of its initial presentation to avoid a reduction in potential earnings. A solution required the correct selection of 3 successive hypertext indices hierarchically structured from the query to the data answer. Under a constant system response time (SRT) condition, each selection of a hypertext index was followed by an 8-second delay before another database level, consisting of both indices and data, was presented.

Under a variable SRT condition, SRTs varied between 1 and 30 seconds, with a mean of 8 seconds. Twenty-five successive queries were presented under each condition, and the order of conditions varied unsystematically across subjects. Systolic blood pressure, mean arterial blood pressure, and heart rate showed pronounced elevations during task performance in comparison to a resting baseline. Diastolic blood pressure and masseter muscle electromyograph (EMG) response did not change reliably over baseline. Intersubject variability in EMG response was, however, related to heart-rate variability during task performance. No differential physiological effects of SRT conditions were observed. An eleventh novice subject's cardiovascular responses habituated over 5 successive performance sessions, but when new queries were introduced, heart rate magnitude increased, showing the reversibility of the effect under novel performance demands.

These data show that tonic cardiovascular responses may be evoked by a time-pressured and realistic human-computer interaction. They also

suggest that work density per unit time is the controlling variable, rather than SRT variability. The laboratory preparation may match functional properties of conditions that prevail in the VDT workplace.

Eleven normal male volunteers have thus far participated in a subsequent investigation, which is in progress. The research protocol replicates the above procedure, but compares physiological effects during constant 1-second and 10-second SRT conditions. Additionally, each subject is typed by the Videotaped Structured Interview (VSI). The data collected thus far indicate that systolic blood pressure is higher during the 1-second condition, in comparison to the 10-second condition, suggesting that work density per unit time is the controlling variable producing cardiovascular effects during time-pressured VDT work. Moreover, scores on the VSI correlate significantly with blood pressure during baseline and task performance. The completion of this protocol will require at least 20 additional subjects to detect physiological differences between Type A and Type B users with a power of .80 at the .05 level of significance.

Publications

Emurian HH: Human-Computer Interactions: Are There Adverse Health Consequences? Computers in Human Behavior, Vol.5, pp 265-275, 1989

Occupational Risks of Pesticide Exposure for Females

William J. Swartz, Ph.D.
Louisiana State University Medical Center
Department of Anatomy
1901 Perdido Street
New Orleans, Louisiana 70112-1393

Program Area: *Disorders of Reproduction*
Grant Number: *5 R01 OH00835-12*
Start & End Dates: *09/01/88 – 08/31/91*
Funding Level: *$59,118 ($533,006 Cum)*

Importance to Occupational Safety and Health

With the advent of increased female participation in the workplace, special attention must be directed toward females who find themselves in occupational settings where exposure to a toxic agent is a reality. It is important to evaluate the effects of a toxic agent on a female and her offspring exposed during pregnancy. However, the intricate and sensitive physiological processes of the reproductive system demand that we look not only at exposure during pregnancy, but that we also direct our attention to exposure of the non-pregnant female who is desirous of having a family one day. Such a comprehensive profile of a specific agent will provide the employer and the employee with data that can safeguard both the immediate and future integrity of the female reproductive system.

Objectives

This study is designed to evaluate the toxicity of the pesticide methoxychlor on the reproductive activity of both pregnant and non-pregnant females. Like previously banned pesticides, DDT and chlordecone, methoxychlor possesses estrogenic activity. Although this estrogenicity has been reported to be less than that exhibited by the banned pesticides, the mere fact that estrogenic activity is present merits serious attention. Since estrogen is a major steroid secreted by the ovary and since proper titers are necessary for normal reproductive activities, any alteration in synthesis, secretion, or target tissue response to this hormone induced by an estrogen-like agent such as methoxychlor could jeopardize immediate and future female fertility. This study is designed to characterize some of the reproductive hazards confronting both pregnant and non-pregnant females engaged in occupations which subject them to potential exposure to estrogenic substances.

Methodology

Adult virgin female CD-1 mice were used in both phases of the experiment. Adult non-pregnant mice (7-10 weeks old) were exposed via oral gavage to specific doses of methoxychlor, estradiol-17β, or sesame oil. After four weeks of exposure, the ovaries were removed and prepared for light and electron microscopical examination and tabulation of the follicle populations. In the experiments involving exposure of pregnant females, mice were exposed daily to the pesticide from Day 6 to Day 15 of gestation. Offspring were evaluated at parturition as to their number, sex, weight, and any visible external malformations. Female offspring ($F1_a$) were cross-fostered among the differently treated mothers and times of vaginal opening recorded. In addition, mothers exposed to the pesticide during their first pregnancy were allowed to mate again following weaning, and their second set of offspring ($F1_b$) was similarly evaluated to detect any residual effects remaining following the initial exposure.

Significant Findings

Electron microscopical studies on ovaries from animals exposed to 5.0 mg methoxychlor for four weeks revealed significant morphological changes when compared to ovaries of sesame oil controls. The most dramatic change occurred in the interstitial compartment with cells containing large amounts of lipid in their cytoplasm. Similarly, there was an increase in the accumulation of lipid and rough endoplasmic reticulum within theca cells surrounding both large atretic and large healthy follicles in ovaries from animals treated with either estradiol or methoxychlor when compared to those of controls.

The methoxychlor and estradiol-treated groups not only showed striking similarities in their ultrastructural characteristics but also in the decreased weight of their ovaries and increased atresia in their large follicles. Thus, the similarity in effects induced by methoxychlor and estradiol would support the reported estrogenicity of methoxychlor. It has been theorized that the high accumulation of lipid in such tissues as corpora lutea indicates a minimal level of steroid release. It is possible that both exogenous estrogen and methoxychlor alter the steroidogenic process with a resultant increase in lipid accumulation. These cells apparently retain their ability to synthesize lipid, but lose their capacity to convert the lipids into steroids. This

alteration in gonadal steroidogenesis could have serious consequences on normal reproductive activity.

In those studies involving exposure of pregnant females to methoxychlor, preliminary data reveal, that there is a higher incidence of atresia in large follicles in females exposed to methoxychlor *in utero* when examined at eight weeks of age than in those exposed to sesame oil. Whether this will affect the fertility of these females is not known. What is known from this study at present is that prenatal exposure to doses of 2.5 and 5.0 mg methoxychlor resulted in no observable effect on number, weight, or sex of the offspring.

Publications

Martinez EM, Swartz WJ: Effects of Methoxychlor on the Reproductive System of the Adult Female Mouse. I. Gross and Histological Observations. Reproductive Toxicology, in press, 1990

Swartz WJ and Mall GM: Chlordecone-Induced Follicular Toxicity in Mouse Ovaries. Reprod Toxicol 3:203-206, 1989

Martinez E and Swartz WJ: Response of the Murine Ovary to Methoxychlor Exposure. Anat Rec, 223:75A. Abstract presented at the 102nd Annual Meeting of the American Association of Anatomists in New Orleans, Louisiana April, 1989

Swartz WJ, Eroschenko VP, Schutzmann RL: Ovulatory Response of Chlordecone (Kepone)-Exposed Mice to Exogenous Gonadotropins. Toxicology 51:147-153, 1988

Swartz WJ, Mattison DR: Galactose Inhibition of Ovulation in Mice. Fertility and Sterility, Vol 49:522–526, 1988

Swartz WJ, Schutzmann RL: Liver Weight Response to Extended Chlordecone Exposure. Bull Environ Contam Toxicol 39:615-621, 1987

Swartz WJ, Schutzmann RL: Reaction of the Mouse Liver to Kepone Exposure. Bull Environ Contam Toxicol 37:169-174, 1986

Swartz WJ, Schutzmann RL: Long-Term Kepone Exposure Reverses Effects on Ovarian Function Induced by Short-Term Exposure. Anat Rec 214:129, 1986 (Abstract)

Swartz WJ, Mattison DR: Benzo(a)pyrene Inhibits Ovulation in Mice. Anat Rec 212:268-276, 1985

Swartz WJ: Effects of Kepone Exposure on Ovarian Function in the Mouse. Anat Rec 211:188A, 1985 (Abstract)

Swartz WJ: Effects of Carbaryl on Gonadal Development in the Chick Embryo. Bull Environ Contam Toxicol 34:481-485, 1984

Swartz WJ: Effects of 1,1-Bis(p-chlorophenyl)-2,2,2-trichlorethane (DDT) on Gonadal Development in the Chick Embryo: A Histological and Histochemical Study. Environ Res 35:333-345, 1984

Adverse Reproductive Events and Electromagnetic Radiation

Walter F. Stewart, Ph.D.
The Johns Hopkins University
School of Hygiene and Public Health
615 North Wolfe Street
Baltimore, Maryland 21205

Program Area: *Disorders of Reproduction*
Grant Number: *1 R01 OH02373-01A1*
Start & End Dates: *09/30/88 – 09/30/90*
Funding Level: *$169,560 ($169,560 Cum)*

Importance to Occupational Safety and Health

Recent studies suggest that exposure to electromagnetic radiation (EMR) is associated with an excess risk of adverse reproductive events, specifically major congenital anomalies and neonatal deaths. Physical therapists (PTs) are frequently exposed to a range of EMR frequencies. A majority of PTs are females of reproductive age, half of whom have experienced some occupational exposure to EMR.

The current study will provide information on the proportion of female PTs ever exposed to EMR, currently or in the past, and evidence on whether there are any reproductive hazards in this group.

Objectives

To determine the risk of reproductive loss and major/minor anomalies among PTs and their offspring, female PTs have been surveyed by mail. The reproductive experience of women, and in particular, fetal loss, will be compared to the reproductive experience of women with little or no

EMR exposure. Both long-term and short-term exposure to EMR prior to and during pregnancies are being considered.

Methodology

All female physical therapists who were current members of the American Physical Therapy Association (APTA) as of July 1988, and all former members since 1975 who had a usable address, have been contacted by mail.

The questionnaire was designed for mass mailing with a specific focus on occupational exposures associated with work as a PT. From our experience in a previous pilot study of 1,500 PTs, a detailed precoded history of exposure to potential sources of EMR surrounding each pregnancy was developed. In addition, precoded questions on reproductive history and exposure to reproductive risk factors were included.

PTs were contacted three times by mail. A questionnaire was sent to all PTs during the first mailing. At that time, PTs were encouraged to complete the questionnaire; but, if for any reason they chose not to respond, they were still encouraged to return the questionnaire. Consequently, we could update the files and prevent another mailing. The second mailing consisted of a reminder postcard to the nonrespondents and was followed shortly thereafter by another questionnaire for the third mailing. From our experience during the pilot study, requesting participants to return the questionnaire regardless of whether they completed it or not increases both the refusal rate (6%) and the response rate (10%) and reduces the number of individuals on whom we have no knowledge.

A 4% random sample of nonresponders has been contacted by telephone and queried on reasons for their nonresponse. A telephone contact was attempted on 500 individuals. Of these, 246 completed the interview, 12 refused, 14 were ineligible to participate (male or nun), 3 were out of the country, and 32 were contacted indirectly through family members but did not return the calls. The remainder could not be reached. They either could have moved or married with a name change. The response rate is similar to that obtained in the mail survey.

Reproductive events among PTs exposed during their pregnancies will be compared to those without EMR exposure. The reproductive events to be considered include fertility, fetal loss, and major/minor anomalies among the offspring. Should a problem be identified among PTs exposed to EMR, more detailed studies will be planned.

Significant Findings

The last mailing for this study occurred on November 11, 1989. As of April 1990, there were 20,773 responses to the mailing, 4,266 undeliverable questionnaires, 3,497 name and address changes still outstanding, and 13,787 nonresponders. Of the 19,114 responders who completed some portion of the questionnaire, 11,598 tried to become pregnant. The remaining 1,659 individuals with whom we made contact included 1,522 refusals; 63 who either died, were too ill to respond, or had moved out of the country; 5 women who claimed to have completed the questionnaire; and 69 with whom we only had telephone contact not followed by a completed questionnaire.

To date, 6,684 of the 11,598 eligible responders have been entered on disk, and the information is being analyzed. These women were selected because they have used microwave or shortwave diathermy (known sources of EMR exposure) at some time in their work history. This was done to minimize the cost and time of processing the information, and to maximize the possibility of observing a relationship, should one exist.

Of the individuals surveyed, 70.4% were between 20 and 39 years of age at the time of the interview, 73% were female, and 95.2% were white. Approximately 74.5% of the responders were current members of the APTA, compared to 62.7% of the total population surveyed. Of the women who have tried or have become pregnant, only 66.1% were less than 40 years of age at the time of interview. Among the women who have used microwave or shortwave during their work history (58%), only 60% were less than 40 years of age at the time of interview. Currently, ultrasound appears to be the favored method of diathermy.

Detailed analyses of the cohort are in progress and should be reported soon.

Occupational Exposures and Birth Defects

Allen A. Mitchell, M.D.
Boston University School of Medicine
Slone Epidemiology Unit
1371 Beacon Street
Brookline, Massachusetts 02146

Program Area: *Disorders of Reproduction*
Grant Number: *1 R01 OH02598-01A1*
Start & End Dates: *02/01/90 - 01/31/92*
Funding Level: *$253,528 ($253,528 Cum)*

Importance to Occupational Safety and Health

In recent years, public and scientific concern over reproductive health has grown substantially. Of all adverse reproductive outcomes, the birth of a malformed child is the most dramatic and has the most serious impact, both from the narrow perspective of the affected family and from the broad perspective of society as a whole. In the last few decades, we have become increasingly aware that environmental agents can cause birth defects in humans. Among occupational exposures, there are many suspected but few confirmed teratogens. In fact, the study of occupational teratogenesis is characterized by profoundly inadequate data. The current project offers a unique opportunity to pursue such needed research. By applying the NIOSH Job Exposure Matrix (JEM) to the Slone Epidemiology Unit's Birth Defects Study (BDS) data base, we will assess the utility of JEM in occupational teratogen research. If we discover that the JEM is not useful in this setting, our finding will help avert fruitless and expensive research efforts, as well as erroneous findings. If these efforts yield a useful data base linking occupational exposures and birth defects, our work will substantially advance this critical area of study.

Objectives

The objective of this project is to establish a large-scale, epidemiologic data resource to facilitate the study of birth defects in relation to occupational exposures. Information will be drawn from the BDS, which has data on over 11,000 infants with a wide variety of birth defects. For each malformed infant, the BDS data base contains information on maternal and paternal occupation and industry. The parents' specific occupational exposures will be ascertained by applying the JEM to these data. By combining data from a large, well-established birth defects surveillance program, we expect to develop a valuable resource for generating and testing hypotheses regarding the risks and safety of occupational exposures.

Methodology

We will develop methods whereby occupational exposures identified by the JEM can be applied to the existing BDS data base in order to develop joint distributions of specific occupational exposures and specific birth defects. These distributions will then be used as a resource for testing and generating hypotheses concerning occupation and birth defects. This research effort consists of three phases. In the first phase, we will use the existing JEM to assign specific workplace exposures to the mothers and fathers of malformed infants within the BDS data file. For the approximately 11,000 malformed infants in the current BDS data base, we have information on job description and occupation at the time of the infant's conception for 99% of mothers and 98% of fathers. For each of these almost 22,000 mothers and fathers, we will develop a profile based on the JEM that identifies (a) all agents to which each parent might have been exposed and (b) for each of those agents, the probability of exposure. To produce this profile, the current BDS job title/industry codes must be translated into codes compatible with the JEM. This process involves developing appropriate algorithms to facilitate direct translation by computer of the BDS codes to their JEM equivalents for those job titles which are sufficiently similar in both systems. For those which are not directly compatible, detailed individual review is required. By the conclusion of this phase, we will determine the numbers of parents exposed to given agents, both to facilitate assessment of the representativeness of this data base and to reflect the statistical power available for further analyses. For each agent, we will identify all job/industry combinations which include any exposure to that agent and calculate the total numbers of fathers and mothers considered by the JEM to be exposed. In this way, we can determine the maximum number of study parents with any exposure to a specific occupational agent.

In the second phase of this project, we will develop the computer software necessary to produce a series of tabulations that will provide frequencies of each listed exposure in each birth defect category, as well as comparisons to the remaining categories of defects. This series of tables will serve as the primary tool for subsequent testing and

generation of hypotheses regarding occupational exposures and birth defects.

In the final phase of the project, we will explore certain aspects of the data in some detail (including previously documented relationships and those first identified within the combined BDS/JEM data set), and thereby provide estimates of the real and potential utility of this new data resource. Based on our assessments of validity for each exposure/birth defect intercept, we will explore various relationships for which there is adequate statistical power.

By the end of the study, we expect to have developed a large and uniquely valuable epidemiologic data resource for studying the relationship of occupational exposures to birth defects. In addition, our experience in assigning specific occupational exposures may serve as a model for application to other data bases, thereby advancing in a more general way the study of occupational hazards.

Significant Findings

None to date.

Prenatal Lead Exposure and Skeletal Growth

John D. Hamilton
University of Cincinnati
Department of Environmental Health
3223 Eden Avenue
Cincinnati, Ohio 45267

Program Area: *Disorders of Reproduction*
Grant Number: *5 R03 OH02376-02*
Start & End Dates: *05/01/87 - 04/30/90*
Funding Level: *$21,003 ($43,653 Cum)*

Importance to Occupational Safety and Health

Although lead is regarded as a potential developmental toxicant, little is known about the mechanisms involved in lead-related effects on important aspects of development, including skeletal growth. This project was designed to investigate the effects of lead on skeletal development.

Objectives

It was hypothesized that lead will adversely alter endochondral bone growth primarily through its interference with chondrogenic activity, not osteogenic activity.

Methodology

The approach taken in the project was to establish a model system of lead-related prenatal and/or postnatal growth retardation in rats, then study the effects of lead on skeletal development in adult rats and their growing offspring, and use a matrix-induced ectopic endochondral bone system to provide information regarding the effects of lead on chondrogenesis and osteogenesis.

Significant Findings

The significant findings were: (1) reduced food intake, not lead exposure, during the first week of lead exposure was the primary determinant of reduced body and skeletal growth (body weight and tail length) in lead-exposed weanling rats; (2) persistence of reduced growth in the same lead-exposed rats was not due to a continuous adverse lead effect on body weight, but to a persistent high correlation between regular growth measurements taken over time; (3) maternal lead exposure had a subtle negative effect on fetal body weight when intrauterine position and sex variables were used along with litter size in the analysis; (4) a greater degree of lead-related growth retardation was found when maternal lead exposure was continued during lactation than when maternal lead exposure was terminated at parturition; (5) continuous maternal lead exposure (prior to mating, during gestation and lactation) caused the greatest degree of weanling offspring growth retardation relative to growth retardation in prenatal-only or lactation-only lead-exposed weanlings; (6) lead altered endochondral bone growth in the epiphyseal growth plate of the proximal tibias in pre- and postnatally lead-exposed weanlings; and (7) whereas the observed lead-related alterations in endochondral osteogenesis appeared to be based on the co-mineralization of lead with calcium, lead-related alterations in endochondral chondrogenesis appeared to be mediated through a lead-related effect on growth plate cartilage matrix maturation. The findings obtained with an ectopic endochondral bone matrix induction system showed that lead applied locally altered normal enchondral mineralization by co-mineralizing with calcium, independently of ectopic bone cellular activity. The

same system demonstrated that lead caused a reduction in growth plate cartilage matrix proteoglycans and glycosaminoglycans that are produced during chondrogenic activity, and which act to inhibit endochondral mineralization. Therefore, the results are consistent with the hypothesis that lead alters cartilage matrix, thereby disrupting enchondral bone growth primarily through its interference with chondrogenic, not osteogenic, activity.

Publications

Hamilton JD, O'Flaherty EJ: Lead Exposure and Skeletal Development. Toxicologist 8:23, 1988 (Abstract)

Adverse Pregnancy Outcomes Among Cosmetologists

David A. Savitz, Ph.D.
University of North Carolina
Department of Epidemiology
CB# 7400
Chapel Hill, North Carolina 27599-7400

Program Area: *Disorders of Reproduction*
Grant Number: *5 R03 OH02548-02*
Start & End Dates: *09/29/87 – 09/28/90*
Funding Level: *$21,675 ($43,425 Cum)*

Importance to Occupational Safety and Health

Cosmetology, a predominantly female employment sector, entails two potential hazards to reproduction: chemical exposures and physical work demands such as prolonged standing. Chemical exposure through inhalation and dermal absorption is of concern since cosmetologists are in daily contact with a variety of cosmetic products such as shampoos, rinses, permanent wave solutions, dyes, relaxers and straighteners, hair sprays, make-up, perfumes, nail polish, artificial nails, detergents, antiseptics, and sterilizing solutions.

Epidemiologic evidence on adverse reproductive outcomes associated with chemical exposures in cosmetology is very limited. No epidemiologic studies have specifically been conducted to examine the risk of adverse pregnancy outcomes in this occupation. Cosmetologists constitute a potentially high risk group with frequent and largely unmonitored chemical exposure. With more than half a million U.S. women employed in cosmetology, many of whom are of childbearing age, the assessment of reproductive hazards in this occupation is warranted.

Objectives

The objective of this study was to assess whether female employment in cosmetology around the time of pregnancy increases the risk of spontaneous abortion, pre-term delivery, or low birth weight. Mothers with adverse outcomes (cases) were compared to mothers with healthy outcomes (controls) with regard to the following exposure categories: work in cosmetology, attendance of cosmetology school, work in other professions, or work as a full-time homemaker. The study further assessed whether the risk of these adverse outcomes varies by intensity of chemical exposure, measured by the number of hours worked per week, and the weekly number of customers, dyes, bleaches, and permanents.

Methodology

A cross-sectional survey was conducted in 1988 among licensed cosmetologists in North Carolina in order to identify women with a pregnancy conceived during a five-year period from 1983 to 1988. Licensed cosmetologists were identified through the computerized license register, which includes both active and inactive cosmetologists. Eligibility was restricted to females aged 22-36 years in 1988. Thus, 8,356 cosmetologists were screened for eligible pregnancies to be included in a case-control study.

Cosmetologists were eligible for the case-control study if their most recent pregnancy was a single live birth or if they experienced a spontaneous abortion between 1983 and 1988. A second questionnaire inquired in more detail about pregnancy outcome, work activities during pregnancy, and other potential risk factors for spontaneous abortion, pre-term delivery, and low birth weight. Stratified analyses and logistic regression modeling were applied to assess the independent relationship between employment in cosmetology and adverse pregnancy outcomes.

Significant Findings

Data collection has been completed and data analysis has begun. The analyses on spontaneous abortions have recently been completed, and analyses on pre-term delivery and low birth weight are currently being conducted. A full report will be available in the spring of 1991.

Publications

John EM, Savitz DA: Effect of a Monetary Incentive on Mail Survey Response. Am J Epidemiol 130:806, 1989 (Abstract)

Physical Activity During Pregnancy and Birth Weight

Anne M. Sweeney, Ph.D.
Michigan State University
College of Human Medicine
Program in Epidemiology
East Fee Hall
East Lansing, Michigan 48824-1316

Program Area: *Disorders of Reproduction*
Grant Number: *5 R03 OH02631-02*
Start & End Dates: *09/30/88 - 09/29/90*
Funding Level: *$18,022 ($36,629 Cum)*

Importance to Occupational Safety and Health

Women of childbearing age represent an increasingly large proportion of the United States work force, comprising 31.6% according to 1984 Bureau of Labor statistics. Increasing numbers of pregnant women are continuing in their employment up until the time of delivery. Little is known concerning the risks and benefits of occupational activity on pregnancy outcome. Several recent epidemiologic studies of the association between occupational activity and birth weight have yielded conflicting results.

Objectives

The aim of this research was to examine the relationship of occupational, leisure time, and household activity during pregnancy to birth weight. The study evaluated the risks and benefits of physical activity in pregnant women through the prospective examination of types and patterns of activity during each trimester and relationships to infant birth weight.

Methodology

The study population consisted of 250 pregnant women from a large womens' hospital in Allegheny County, Pennsylvania. Subjects were identified in a consecutive manner as they reported for prenatal care. Data collected included demographic characteristics, medical/reproductive history, occupational and environmental exposures, behavioral factors (smoking, alcohol, and drug use), and any illnesses which occurred during the pregnancy. Data were collected by phone or during a prenatal visit at the clinic, per subject preference. An assessment was made of a woman's total daily physical activities by determining the three major components of activity: occupational, leisure time, and household activity. Occupational activity was assessed by an adapted version of the CDC-Behavioral Risk Factor Surveillance Form, which was designed to address the key issues of physically demanding job tasks, as well as the amount of time spent sitting and standing still at work. The Paffenbarger survey was adapted to determine the subjects' leisure time and household activities. This survey was tested for reliability in a subsample of the population, with test-retest correlations of .80. Average weekly kilocalorie expenditure levels for each of the three types of activity were calculated per subject per trimester, as well as the sum of these three components to represent an average weekly total kilocalorie expenditure level per trimester.

Data abstraction from the medical records included ultrasound examination for the calculation of gestational age; birth weight; maternal weight at the end of each trimester (or at delivery); number of prenatal visits; and labor and delivery complications.

Univariate analyses were run on both the total sample and by race to determine relationships between birth weight and the demographic, behavioral, and medical history variables, and between birth weight and each of the physical activity characteristics. Race-specific tests of trend for mean birth weight across quintiles of physical activity levels were conducted. Finally, race-specific multiple linear regression analyses were done to determine the independent effect of physical activity and birth weight while controlling for confounders.

Significant Findings

A total of 221 women (84.4%) had delivered at the time of this writing. Only 30 of these women were recruited from private obstetricians' offices. The present analysis focussed on the clinic population of 189 women. Fifty-two percent were black; 42% white. Forty percent of the women worked outside of the home at some point during pregnancy; employment status did not differ statistically by race. Sixty-three percent had an income level of <$10,000/year; 73% were not married; and 59% had a high school education or

less. Fifty-four percent of the white women smoked compared to 38% of the black women ($p = .04$); the proportion reporting alcohol consumption did not differ by race. There were no significant differences in pre-pregnant weight or weight gain during pregnancy between blacks and whites. Black women had a mean of 1.38 children compared with .798 among white women ($p < .001$), and more black women had a previous live birth(s) > 5 pounds ($p = .008$). The mean birth weight for black infants was 191 grams less than that of white infants (3153 grams vs 3344 grams respectively, $p = .004$). Gestational age (in weeks) was shorter in blacks (38.4 compared to 39.5 for whites, $p < .001$).

There were no significant differences in total average weekly kilocalorie expenditure levels by race in any of the trimesters. There was an overall decrease in physical activity level as pregnancy progressed in both races. Activity-specific analysis revealed that in general, white women had higher occupational kilocalorie expenditures. However, in the univariate analysis no significant relationships between any of the activity components and birth weight were seen in the white women. Among blacks, both occupational and household kilocalorie expenditure in the third trimester showed a significant inverse relationship to birth weight.

Race-specific tests of trend revealed a pattern of decreasing birth weight with increasing levels of physical activity in blacks in the third trimester. Although not statistically significant, infants born to women in the most physically active group had a mean birth weight 126 grams lower than the infants of mothers in the least active quintile. There was no such relationship seen in the white women. After controlling for gestational age, maternal height, pre-pregnant weight, gestational weight gain, and smoking, race-specific multiple regression analysis revealed that total average weekly kilocalorie expenditure was an independent predictor of birth weight among black women in the second and third trimesters. Physical activity was not a predictor of birth weight in white women in any trimester.

These data suggested that the mechanism through which physical activity may affect birth weight is by decreasing gestational length. This relationship needs to be evaluated in a larger sample with greater variability in gestational ages.

Occupational Neuropathies Due to Industrial Chemicals

Mohamed B. Abou-Donia, Ph.D.
Duke University Medical Center
Department of Pharmacology
Durham, North Carolina 27710

Program Area: *Neurotoxic Disorders*
Grant Number: *5 R01 OH00823-10*
Start & End Dates: *01/01/86 - 12/31/89*
Funding Level: *$162,873 ($1,173,869 Cum)*

Importance to Occupational Safety and Health

Neuropathies resulting from occupational exposure to one chemical or multiple compounds have been documented. The mechanism underlying the neurotoxic action of several industrial chemicals involves the accumulation of neurofilaments. These chemicals include n-hexane and its metabolites, 2-hexanone (MnBK) and 2,5-hexanedione (2,5-HD), carbon disulfide (CS_2), and delayed neurotoxic organophosphorus compounds, e.g., tri-o-cresyl phosphate and EPN. Human exposure to n-hexane and CS_2 is mostly limited to work place. n-Hexane and MnBK are used in the textile industry, while CS_2 is used in vicose rayon, vicose film, and nylon-polyester industries. Worldwide, approximately 2.1 million and 1.1 million persons are exposed to n-hexane and CS_2, respectively. Humans may be exposed to organophosphorus compounds in the work place, as well as various sources such as drinking water, air, or food. In 1981, more than 396.5 million pounds of phosphorus-containing compounds were produced in the United States. This includes over 50,000 pesticides used as insecticides, acaricides, fungicides, or cotton defoliants.

Objectives

The overall objective of this project is to study the mechanism(s) of the joint neurotoxic action resulting from exposure to multiple chemicals. The goal of the studies is to develop specific biomarkers for exposure to neurotoxicants, by studying the target proteins in the nervous system and liver microsomal xenobiotic metabolizing enzymes.

Methodology

The animal of choice to study organophosphorus compound-induced delayed neurotoxicity is the adult hen since rodents are less sensitive. The hen is also sensitive to neurotoxicity induced by aliphatic hexacarbons. The morphology and distribution of the neuropathic lesions induced by both classes of chemicals have been characterized in this animal model. Cytoskeletal proteins are being studied as a target for neurotoxicities induced by these chemicals. Also, the role that liver microsomal cytochrome P-450 isozymes play in the activation and detoxification of neurotoxic chemicals is under investigation.

Significant Findings

We have shown that although organophosphorus compounds and n-hexane chemicals produce similar clinical features in the hen, they have distinct morphology and distribution of the neuropathologic lesions. Concurrent exposure to dermal EPN and MnBK vapor resulted in potentiation of their neurotoxic action. Also, neurotoxicity of the weak neurotoxicant n-hexane was synergized by non-neurotoxicant methyl iso-butyl ketone (MiBK). Similarly, simultaneous dermal exposure to EPN and n-hexane and its metabolites resulted in additive or potentiating effects. The joint neurotoxic action of organophosphorus compounds and n-hexane may have resulted from the induction of hepatic cytochrome P-450. Also, n-hexane and its metabolites may have enhanced dermal absorption of EPN. Neurotoxicity resulting from simultaneous exposure to n-hexane and MiBK was characterized by cross-linking of the three neurofilament triplet proteins; 70 kDa, 160 kDa, and 220 kDa in the spinal cord. Ca^{2+}-calmodulin-dependent kinase phosphorylation of these proteins was also diminished. Acute cholinergic and delayed neurotoxic effects of EPN were increased by simultaneous treatment with n-hexane and MiBK. Inhalation of MiBK, or a mixture of MiBK and n-hexane, induced liver microsomal cytochrome P-450 and increased the oxidation of EPN to EPN oxon. Two cytochrome P-450 isozymes (P-450 PB-A and PB-B) and cytochrome b_5 were purified to electrophoretic homogeneity from livers of phenobarbital-treated adult hens. Both isozymes have the apparent molecular weight of 54 kDa by SDS-PAGE. The antibodies raised against P-450, PB-A, and PB-B neither cross-reacted with each other nor with microsomal P-450s of rat, mice, cat, or catfish by immunoblotting. Also, four cytochrome P-450 isozymes (β-NFA, β-NFB, β-NFC, and β-NFD) were purified and

characterized by β-napthoflavone-treated adult hens. Hens exposed to toluene vapor (1,000 ppm) neither developed neurologic dysfunction nor neuropathologic lesions. Also concurrent exposure to toluene and n-hexane or MiBK did not produce neurotoxicity.

Publications

Abou-Donia MB, Lapadula DM: Mechanisms of Organophosphorus Ester-Induced Delayed Neurotoxicity: Type I and Type II. Annu Rev Pharmacol Toxicol 30:405-440, 1990

Gupta RP, Lapadula DM, Abou-Donia MB: Purification and Characterization of Cytochrome P-450 Isozymes from Phenobarbital-Induced Hen Liver. Comp Biochem Physiol 96C:163-176, 1990

Gupta RP, Lapadula DM, Abou-Donia MB: Purification and Characterization of Cytochrome P-450 Isozymes from β-napthoflavone-Induced Hen Liver. Arch Biochem Biophys 282:170-182, 1990

Abou-Donia MB, Lapadula DM: Cytoskeletal Proteins and Axonal Neuropathies. Comme Toxicol 3:427-444, 1989

Abou-Donia MB, Lapadula DM: Studies on the Pathogenesis of Organophosphorus Compound-Induced Delayed Neurotoxicity (OPIDN). In: Insecticide Action, (eds. T Narahashi, JE Chambers), Plenum Publishing Corporation, pp 205-216, 1989

Lapadula DM, Suwita E, Abou-Donia MB: Evidence for Multiple Mechanisms Responsible 2,5-Hexanedione-Induced Neuropathy. Brain Res 458:123-131, 1988

Abou-Donia MB, Lapadula DM, Suwita E: Cytoskeletal Proteins as Targets for Organophosphorus Compound and Aliphatic Hexacarbon-Induced Neurotoxicity. Toxicology 49:469-477, 1988

Somkuti SG, Tilson HA, Brown HR, Campbell GA, Lapadula DM, Abou-Donia MB: Lack of Delayed Neurotoxic Effect after Tri-o-Cresyl Phosphate Treatment in Male Fischer 344 Rats: Biochemical, Neurobehavioral, and Neuropathological Studies. Fund App Tox 10:199-205, 1988

Carrington CD, Abou-Donia MB: Variation Between Three Strains of Rat: Inhibition of Neurotoxic Esterase and Acetylcholinesterase by Tri-o-Cresyl Phosphate. J Tox Env Health 25:255-264, 1988

Carrington CD, Brown HR, Abou-Donia MB: Histopathological Assessment of Triphenyl Phosphite Neurotoxicity on the Hen 9(2):233-234, 1988

Lapadula DM, Irwin RD, Suwita E, Abou-Donia MD: Crosslinking of Neurofilament Proteins of Rat Spinal Cord *In Vivo* after Administration of 2,5-hexanedione. J Neurochem 46:1843-1850, 1986

Abou-Donia MB, Lapadula DM, Campbell GA, Timmons PR: The Synergism of n-Hexane-Induced Neurotoxicity by Methyl Iso-butyl Ketone Following Subchronic (90 Days) Inhalation in Hens: Induction of Hepatic Microsomal Cytochrome P-450. Toxicol Appl Pharmacol 81:1-16, 1985

Abou-Donia MB, Lapadula DM, Campbell GA, Abdo KM: The Joint Neurotoxic Action of Inhaled Methyl Butyl Ketone Vapor and Dermally Applied O-Ethyl, O-4-Nitrophenyl Phenylphosphonothioate in Hens: Potentiating Effect. J Toxicol Appl Pharmacol 79:69-82, 1985

Peripheral Markers of Styrene Toxicity

Harvey Checkoway, Ph.D.
University of Washington
Department of Environmental Health, SC-34
Seattle, Washington 98195

Program Area: *Neurotoxic Disorders*
Grant Number: *5 R01 OH02629-02*
Start & End Dates: *12/01/88 – 11/30/90*
Funding Level: *$120,617 ($272,792 Cum)*

Importance to Occupational Safety and Health

Adverse effects from occupational chemical toxicants typically are only detected when related health outcomes are severe following periods of intense exposure. Morbidity and mortality are the usual indicators of toxicity. Effects to the nervous system increasingly are being recognized as important endpoints for epidemiologic and clinical research in the workplace. There is also a growing trend in occupational health research to develop and validate methods for early detection of biochemical changes caused by toxic workplace exposures. The

goals of this approach are to assess potential risks to health before overt morbidity occurs and to reduce or eliminate hazardous agents from the workplace. Biological monitoring is the term often used in this context. Biological monitoring can consist of measurement of toxicants, determination of biological response to toxic exposures, or determination of genetically-determined host factors that render persons more or less susceptible to toxicity. This project involves the application of exposure and biological response biomonitoring among workers exposed to the industrial neurotoxicant, styrene. Peripheral blood and urine are used as the media for exposure biomonitoring, and peripheral blood cells are assayed for response to styrene. If the biomonitoring methods developed in studies such as the present investigation prove to be applicable for epidemiologic research, then this strategy will be a valuable approach for detection and prevention of chemical-induced toxicity.

Objectives

The overall objectives of this research are: (1) to explore the utility of biomarkers of neurochemical function and chemical detoxification potential, using peripheral blood cells as indicators of response in target tissues; (2) to examine exposure-response relationships between levels of peripheral biochemical markers and various exposure indicators; (3) to assess relationships between biomarker levels and prevalence of central nervous system (CNS) symptoms; (4) to examine exposure-response relationships for liver transaminases; and (5) to test the utility of exposure biomarkers, blood styrene levels, and urine metabolite levels measured at convenient rather than optimal sampling times.

The biomarkers used to assess neurochemical function are serotonin (5HT) uptake and monoamine oxidase type B (MAO-B) in platelets, and sigma receptors in lymphocytes. Prior experimental evidence suggests that styrene may deplete dopamine in the brain, thus resulting in a decrease of MAO-B which catabolizes dopamine. Serotonin uptake may be perturbated, as suggested by prior animal evidence and studies of workers exposed to mixed solvents. Two chemical detoxification enzyme systems, glutathione-S-transferase (GST) and epoxide hydrolase (EH), are being measured in peripheral lymphocytes. Distortions in GST activity could result from glutathione depletion, a phenomenon that has been shown with rats. EH activity, which protects the liver form many xenobiotic compounds, would be impaired, possibly in response to styrene metabolites, principally styrene oxide. Liver function is determined from serum values of SGOT, SGPT, and SGGT.

Methodology

This study involved a repeated measures design in which blood and urine samples were obtained from styrene exposed workers and a non-exposed reference group at two points in time. Exposed workers were identified from three reinforced fiberglass plastics plants, and the non-exposed workers were identified from truck engine assembly workers not exposed to solvents. The study included 78 exposed workers and 18 reference workers at Survey 1. Fifty-eight (58) of these workers participated at Survey 2. An additional 8 exposed workers were included at the second survey.

Two surveys were conducted, the first in May, 1989, and the second in October, 1989. At the first survey, a questionnaire was administered eliciting data on demographics, work history, alcohol use, smoking, and medical history, including recent nervous system symptoms. At both surveys, 8-hour time weighted average breathing zone air concentrations of styrene were measured by personal monitoring using passive diffusion badges. Also, blood samples were obtained for styrene concentration measurements, and urine samples were assayed for styrene metabolites, and mandelic and phenylglyoxylic acids. Sigma receptor binding was assayed against three ligands: 3-H-Spiperone, Haloperidol and di-toluyl-guanidine (DTG). MAO-B activity and 5HT uptake in platelets were assayed using standard techniques. GST and EH activities in lymphocytes were determined using benzo(a)pyrene as the substrate.

Significant Findings

Comparative analyses of styrene air concentrations, urine metabolites, and blood styrene concentrations revealed high degrees of correlation at both surveys (r-values ranging from 0.6-0.9). This suggests that biological monitoring at convenient times (i.e., mid-shift) can provide meaningful results. Blood styrene levels were used as the primary exposure indicator in the analyses of the symptom and biomarker data. Increasing trends of prevalence with increasing blood styrene levels were detected for the following CNS symptoms: headaches, dizziness, light-headedness, fatigue, irritability, memory loss, and feeling "drunk" at work, as well as for numbness or tingling in the hands and feet. These findings are consistent with previous literature. With respect to the biomarker data, no consistent trends were noted for sigma

receptor binding, GST, or EH. MAO-B was inversely correlated with blood styrene level, whereas a slightly positive correlation was noted for serotonin uptake. A provocative finding was the relationship between MAO-B and prevalence of CNS symptoms. From the first survey, mean values of MAO-B (adjusted for age, gender, race, alcohol use, smoking, and employment duration) were 26.4, 46.4, 16.9, and 5.5, respectively, for subjects reporting 0, 1, 2, and 3 or more CNS symptoms. Symptom prevalence was not determined at Survey 2; thus, this association could not be evaluated. Liver transaminases did not appear to be affected by exposure level.

Publications

Checkoway H, Costa LG, Coccini T, Rappaport SM, Manzo L: Monitoring Styrene Neurotoxicity with 3-H-Spiperone Binding in Lymphocytes. In: Occupational Epidemiology: Proc of the Seventh International Symposium on Epidemiology in Occupational Health, (eds. H Sakurai, I Okazaki, K Omae), Amsterdam: Excerpta Medica, pp 197-200, 1990

Dills R, Kent SD, Checkoway H, Kalman DA: Quantitation of Volatile Solvents in Blood Using Static Headspace Analysis. Talanta, in press, 1990

Neurologic Effects of Solvents and Age in Older Adults

William Daniell, M.D., M.P.H.
University of Washington
Occupational Medicine Program
SC-34
Seattle, Washington 98195

Program Area: *Neurotoxic Disorders*
Grant Number: *5 R01 OH02683-02*
Start & End Dates: *09/30/89 - 09/29/91*
Funding Level: *$166,820 ($391,937 Cum)*

Importance to Occupational Safety and Health

A number of cross-sectional epidemiologic studies have demonstrated functional abnormalities of the central nervous system among solvent-exposed working populations. However, the differences have generally been subclinical, and their long-term significance has not been characterized. There is evidence that aging-related processes may latently interact with the effects of subclinical central nervous system injury, such as former solvent exposure, to result in neurologic dysfunction which is clinically significant and disproportionately greater than that which might result from either variable alone. Older, retired adults who were routinely exposed to solvents during their working years may therefore be at increased risk for significant neurologic problems attributable to their former work even though such problems may have been unapparent during the earlier periods of solvent exposure.

Objectives

The study is addressing the following questions:

1. Are there decrements in neurologic function among retired painters relative to a control population (retired carpenters)?
2. Does neurologic function show any biologically plausible, adverse relationship to measures of recalled past solvent exposure, and can any such relationships be explained by latency or threshold effects?
3. Is there any evidence that alcohol consumption interacts with solvent exposure to influence neurologic function?
4. Are there intergroup differences among selected non-neurologic areas of function?

Methodology

The study is using a cross-sectional design to examine neurologic function (subjective, neurosensory, neuropsychological, and psychiatric parameters) among retired painters in comparison to a similarly examined control group. The control group consists of retired workers with similar professional backgrounds but only incidental past exposures to organic solvents or other neurotoxins (carpenters). Neurologic function will be further evaluated relative to semiquantitative indices of recalled past solvent exposure. Nonneurologic parameters, including blood tests of liver function, blood and urine measurements of renal function, respiratory symptoms, and spirometry are also being examined as outcomes of secondary interest.

Significant Findings

Data collection is in progress. No results are available.

Central Nervous System Effects of PCE Exposure in Humans

Diana Echeverria, Ph.D.
Battelle Human Affairs Research Center
4000 N.E. 41st Street
Seattle, Washington 98105

Program Area: *Neurotoxic Disorders*
Grant Number: *1 R01 OH02719-01*
Start & End Dates: *02/01/90 - 01/31/93*
Funding Level: *$233,100 ($233,100 Cum)*

Importance to Occupational Safety and Health

This project examines the relationship between chronic exposure to perchloroethylene (PCE) and symptoms, neurobehavior, and neurophysiologic central nervous system (CNS) effects in workers. These effects are being evaluated in dry cleaners chronically exposed to different levels of PCE using never-exposed laundry workers as a reference group.

The study documents a possible continuum from subclinical to clinical CNS effects following exposure to PCE in one of the few industrial populations frequently exposed to high levels above 40 ppm. At the completion of the study, the prevalence of chronic CNS effects will be thoroughly characterized between 0 and 100 ppm, and the lower threshold for adverse symptoms, behavior, and physiologic effects will be known at the proposed OSHA PEL of 25 ppm.

Objectives

Based on a pilot study, a frontal/limbic system behavioral hypothesis is offered as the site of underlying pathology for subclinical PCE effects. Alternatively, potential deficits could be related to hippocampus and brain-stem activity assessed separately by neurophysiologic electro-encephalograms and visual evoked potentials.

Methodology

The cross-sectional CNS evaluation will be conducted on 84 never-exposed laundry workers, 42 low, 42 moderate, and 84 highly exposed dry cleaner employees in the Seattle, Washington area. To control for acute exposure effects, the symptom and behavioral evaluation will be conducted over 3 sessions; on the afternoon of their day off, 36 hours post-exposure in the morning at their work site, and again at the end of the workshift.

The core behavioral battery will include the following tests:

Function	Mode	Test	Method
Motor:	MD	One Hole	C
Attention:	VS	NES Digit Span	C
	VB	Oral Digit Span	P
Cognitive	VS	Trial Making	P
Flexibility:	VB	PASAT	P
Reasoning:	VS	Similarities	P
	VB	Wis card sort	P
Memory			
Short Term:	VS	Pattern Memory	C
	VS	Visual Repro	P
	VB	Cal Verb Learn	P
Mood	VS	POMS	P
	VB	POMS	P
Basic Skill	VC	Vocab	C
	M	Arith	C
Add ons	VS	Switch	C
	VS	Color Hue	P
	VS	Pattern Recognition	C

C = Computerized
M = Math
MD = Manual Dexterity
P = Paper
VB = Verbal
VC = Vocabulary
VS = Visual

A pre-exposure alveolar breath sample will be measured to control for variation in PCE body burden, supplementing 8-hour air monitoring for each exposed worker and one of every eight non-exposed workers. Exposure zones will be based on (1) distance from PCE source, (2) PCE air levels, and (3) PCE breath levels. Peak sampling will be conducted on operators with fluctuating exposures estimated to affect brain PCE levels. These exposure measures will be used to construct lifetime indices of cumulative exposure. The 2-hour neurophysiologic assessment will occur at least 24 hours post-exposure on a separate day. Paid volunteers will be 18 to 65 years old, English speaking, and will have had no history of CNS disorders. No subjects will be excluded on the basis of alcohol consumption since interaction between PCE and alcohol is a research interest. The immediate influence of caffeine and alcohol will be controlled. To evaluate the exposure-effect within each shop, volunteers from each exposure zone will be tested. Potential confounding effects of age and education will be controlled by measures of

stratification and multiple regression. To evaluate acute CNS effects, the high and the non-exposed group will be tested pre- and post-exposure. To estimate the degree of potential job selection bias in testing healthy workers, 42 previously exposed workers will also be followed-up from 10-year-old employment rosters and evaluated for symptoms and behavioral effects.

Significant Findings

Work frequently requires switches of attention between job tasks. Such switching can involve a time cost beyond that required to continuously perform single tasks. A new test was introduced into the CNS PCE battery to evaluate the ability to serially switch between three comparison tasks.

Two preliminary studies were completed in the first year of this project to examine the effect of age and ethanol on switching between tasks. The studies would provide some validity of its use as a chronic or acute neurobehavioral measure for the PCE and other solvent studies, as well as provide a measure of test/retest reliability and estimates for statistical power calculations. Production workers at two research facilities, between the ages of 18 and 70, were stratified into 5 age groups and tested pre- and post-shift. The age-study ($n=104$) found significant effects of age, tasks, repetition, and an interaction of preceding task on the current task or switching ($p < .0001$). The ethanol study (5 exposed and 20 unexposed but age and education matched subjects drawn from the age study) found increases in the times to switch between dissimilar tasks ($p<.03$). The switching task was thus found to have excellent psychometric properties and sensitivity to chronic and acute environmental factors. The switching task was therefore included in the PCE battery and recommended for future solvent studies of CNS behavioral effects in industrial settings.

Publications

Toutonghi G, Echeverria D, Bittner A, Ronhovde N: The Use of Switching Ability to Assess Central Nervous System Function. Industrial Ergonomics and Safety, Vol 3, Taylor and Francis, London, 1991

In Vitro Glial Responses to Halothane Metabolite, TFA

Michael T. Tseng, Ph.D.
University of Louisville
Department of Anatomical Sciences and Neurobiology
Louisville, Kentucky 40292

Program Area: *Neurotoxic Disorders*
Grant Number: *5 R03 OH02578-02*
Start & End Dates: *04/01/88 - 03/31/90*
Funding Level: *$21,825 ($43,589 Cum)*

Importance to Occupational Safety and Health

A glycoprotein moiety of the C6 glioma cell surface with an approximate molecular weight of 92,500 daltons has been identified as a potential surface membrane target for trifluoroacetic acid (TFA). This protein may be a common binding site for the inhalation anesthetics and could be useful in detecting the presence of occupational hazards involving the use of halogenated alkanes and alkenes.

Objectives

The long-term objective for the proposed research is to elucidate the mechanism by which the chronic exposure of very low concentrations of inhalant anesthetics leads to the development of neuronal lesions. The specific aims for the current experiments are to determine the impact of TFA, the principal oxidative metabolite of halothane, on DNA, protein, and glycoprotein synthesis, as well as the cellular aggregation in C6 glioma cells.

Methodology

Cell culture and TFA exposure: C6 glioma was chosen as the model for this study and was obtained from ATCC (Bethesda, MD). The cells were maintained as a monolayer in RPMI 1640 medium supplemented with 5% fetal bovine serum and antibiotics in a humidified CO_2 incubator at 37° C. TFA at concentrations between 0-10 mM were dissolved in the culture media and the monolayer cultures were exposed for 24 h. At the end of incubation, cells were washed and removed for SDS gel electrophoresis or other analytical procedures.

Cell agglutination assay: After the TFA treatment, C6 cells were removed and suspended in

PBS at concentration of 4° C. The average concentration of cell volume was 5 x 10^6. Among the lectins tested, *Ricinus communis* agglutinin consistently aggregated the cells. A dose-dependent response was seen in TFA treated C6 cells in the presence of this lectin between 0-50 g. To determine the rate of change of absorbance at 546 nm, the contents of the cuvettes were rapidly mixed and placed in the chamber of a Gilford Response II spectrophotometer.

Identification of the cell surface moiety affected by the TFA treatment by SDS gel electrophoresis. Twenty-four hours after 10 mM TFA exposure, cells were labeled with 50 ci of D-[^{3}H] mannose in glucose-free 1640 medium for 2 h. Cells were washed with Ca^{++}, Mg^{++}-free phosphate buffered saline, freeze-thawed four times, and centrifuged. The pellet was mixed with an equal volume of sample buffer (10% glycerol, 5% 2-mercaptoethanol, 30% SDS, 0.75% Tris, and a trace of bromophenol blue) and denatured by boiling at 100° C for 3 minutes. Aliquots of samples were added to a 7.5% slab SDS polyacrylamide gel. After running for 5 h at 150 v, the gels were fixed with methanol for 30 minutes. After staining with 0.075% Coomassie brilliant blue and overnight destaining with 10% acetic acid followed by 10% methanol, the gels were soaked in Fluro-enhance autoradiography enhancer for 30 minutes dried on a Bio-Rad gel dryer, covered with Kodak X-Omat AR films, and exposed for 5 weeks at 70° C. The density of the polypeptide bands were analyzed with a CS-900 dual wave length Flying Spot Scanner (Shimadzu Corp., Japan).

Further characterization of the labeled proteins by two dimensional PAGE. The procedure on isoelectric focusing (IEF) in the disc gel was carried out according to the method of O'Farrell. IEF gels were run for 8,400 V.h. in 4% pH 5-7, 2% pH 6-8, 2% pH 3.5-10 ampholines. Two dimensional electrophoresis was run for 800 V.h. in gels that contain 5-16% exponential gradient slab SDS-polyacrylamide. After staining with Commassie brilliant blue, the gels were destained, dried, covered with X-ray film and processed for autoradiography as described above.

Significant Findings

Under the experimental protocol, the treatment of TFA minimally affected the cell growth or the general protein synthesis. However, TFA affected the rate of lectin-induced cell agglutination. This surface membrane change is corroborated by the finding of TFA-inhibited glycosylation of a protein moiety with an apparent molecular weight of 92,500 dalton. This glycoprotein, when fully characterized, may prove to be one of the targets through which the harmful effects of the halogenated alkanes or alkenes are being expressed.

Publications

Ma TG, Ling YH, McClure GD, Tseng MT: Effects of Trifluoroacetic Acid, A Halothane Metabolite, On C6 Glioma Cell. J Toxicol Environ Health 31:147-158, 1990

The Effects of Impulse Noise on the Auditory System

Donald Henderson, Ph.D.
State University of New York
215 Parker Hall
Buffalo, New York 14214

Program Area: *Noise-Induced Hearing Loss*
Grant Number: *7 R01 OH01152-09S1*
Start & End Dates: *07/01/80 - 09/28/90*
Funding Level: *$194,938 ($1,127,104 Cum)*

Importance to Occupational Safety and Health

Impulse and impact noise found in industry constitutes a special hazard to workers' hearing. For equivalent amounts of acoustic energy, impulse and impact noise may cause significantly more hearing loss than exposure to continuous noise. There is consensus that current noise standards are completely inadequate for protecting workers from exposure to impulse and impact noise. Our research is trying to understand the biological basis of impulse noise-induced hearing loss. From a practical perspective, the research is directed at learning the range of parameters of impulse and impact noise that contribute to making an exposure hazardous. The results of this research will serve as part of the scientific foundation of more comprehensive noise standards.

Objectives

The research program has three complementary objectives: (1) to understand the relation between the parameters of impulse/impact noise (peak pressure, duration, number, repetition rate, exposure duration, spectrum) and the effects on hearing; (2) to understand the complicated series of changes in the inner ear following traumatic exposures; and (3) to explore the possibility that "priming" exposures to non-traumatic noise can reduce the amount of hearing loss from a dangerous noise exposure.

Methodology

Several mechanical or electrical-mechanical devices are used to produce realistic noise impacts. Hearing is tested, the animal is exposed to impulse/impact noise, and its hearing is tested for the following forty days. Routine data collection consists of measurements of hearing sensitivity, auditory discrimination, and cochlear histology. More detailed studies of certain experimental groups will include scanning E.M., as well as more discriminating psychoacoustic measures of hearing.

Significant Findings

Since the inception of this project, we have reported a number of findings. (1) Certain combinations of impulse and continuous noise constitute an especially hazardous situation. (2) Exposures above a certain "critical" level cause direct mechanical damage. This project has begun to document how the critical level varies with the parameters of the impact/impulse. In addition, microscopic studies have elucidated the complicated series of changes that occur in the inner ear following exposure to traumatic levels of impulse and impact noise. (3) The project has developed a number of psychoacoustic tests that better characterize the hearing impairment caused by dangerous noise. (4) The project has shown the damaging effects of noise can be exacerbated with other agents, i.e., vibration and certain drugs. (5) Recent work has shown how exposure to non-damaging noise may actually protect the subject from further exposure to dangerous noise. All of these results have direct implications for the management of workers in noisy environments.

Publications

Byrne C, Henderson D: Synergistic Effects of Whole Body Vibration and Noise on Hearing in the Chinchilla. J Acoust Soc Am, in press, 1991

Campo P, Subramaniam M, Henderson D: Effect of Low-Level Pre-exposures on Hearing Loss from Traumatic Exposure. Hearing Research, in press, 1991

Subramaniam M, Campo P, Henderson D: The Effect of Exposure Level on the Development of Progressive Resistance to Noise. Hearing Research, in press, 1991

Dancer A, Henderson D, Salvi R, Hamernik RP: The Effects of Noise on the Auditory System. B.C. Decker, Hamilton, Ontario, Canada, 1991

Henderson D, Mills J, Colletti V: Psychophysical Performance in Normal and Impaired Ears. In: Otolaryngology, (eds. Paperallea, Meyerhof), Saunders, Philadelphia, pp 255-268, 1991

Henderson D, Campo P, Subramaniam M, Fiorino F: Development of Resistance to Noise Induced Hearing Loss. Paper presented at the IV International Conference on the Effect of Noise on the Auditory System, Beaune, France, May 28-30, 1990

Henderson D, Danielson R, Farzi F: The Critical Level Concept and Impulse Noise. Noise as a Public Health Problem, Stockholm, Sweden, Environmental International, Vol 16, pp. 353-361, 1990

Henderson D, Subramaniam M, Saunders S: Impact Noise: The Importance of Level, Duration, and Repetition Rate. J Acoust Soc Am, in press, 1989

Fiorino FG, Gratton MA, Subbanna M, Bianchi L, Henderson D: Physiological Mechanism Underlying the Progressive Resistance to Noise Induced Hearing Loss. Paper presented at the 2nd International Symposium on Cochlear Mechanics and Otoacoustic Emissions, Rome, Italy, March 9-11, 1989. IL Valsalva, 54 (suppl 1):36-41, 1989

Boettcher FA, Henderson D, Gratton MA, Byrne C, Bancroft B: Recent Advances in the Understanding of Noise Interactions. Archives of Complex Environmental Studies 1(1):15-21, 1989

Henderson D, Danielson RW, Saunders SS: Influences of Temporal Spacing of Impulse Noise on Temporary and Permanent Threshold Shifts. 115th Meeting of the Acoustical Society of America, Seattle, WA, May 1988

Byrne C, Henderson D, Saunders S, Powers N, Farzi F: Interaction of Noise and Whole Body Vibration. Recent Advances in Research on the Combined Effects of Environmental Factors, (ed O. Manninen), Pk-Paino Oy Printing HOuse, Tampere, Finland, pp 239-268, 1988

Byrne C, Henderson D, Saunders S, Powers N, Farzi F: Interaction of Noise and Whole Body Vibration. Proceeding of Third International Conference on Combined Effects of Environmental Factors, Tampere, Finland, 1988

Danielson R, Henderson D: Temporal Pattern of Impulse Noise: Implication for the Equal Energy Hypothesis. Proc of Symposium on Noise as a Public Health Problem, Stockholm, Sweden, Vol 2, 1988

Henderson D, Hamernik RP: A Parametric Evaluation of the Equal Energy Hypothesis. In: Basic and Applied Aspects of Noise-Induced Hearing Loss, (eds. R Salvi, D Henderson, RP Hamernik), Plenum Press, New York, 1988

Gratton MA, Salvi RJ, Kamen BA, Henderson D, Poon M: Combined Effects of Noise and Cisplatin: Effect on Hearing. Recent Advances in Researches on the Combined effects of Environmental Factors, (ed. O Manninen), pp 255-268, 1988

Henderson D, Arehole S, Gopal HS: Psychophysical Change with Sensorineural Hearing Loss. In: Clinical Audiology, (ed A Quaranta), Laterza Press, Bari, Italy, 1987

Henderson D, Arehole S, Salvi RJ, Saunders SS: Temporary Hearing Loss: Effects on Evoked Response "Forward Masking" Functions in the Chinchilla. Hearing Res 27:193-205, 1987

Henderson D, Colletti V, Sittoni V: The Role of the Acoustic Reflex in Noise-Induced Hearing Loss. In: Clinical Measurement of Acoustic Impedance, (ed. V Colletti), Amplaid, Milano, 1987

Henderson D, Danielson R, Saunders S, Anderson C: Wide-Band Multi-Frequency Middle Ear Impedance Measurement. In: Clinical Measurement of Acoustic Impedance, (ed. V Colletti), Amplaid, Milano, 1987

Henderson D, Gratton MA, Salvi RJ: Interaction of Cisplatinum and Noise. In: Clinical Audiology, (ed. A Quaranta), Laterza Press, Bari, Italy, 1987

Henderson D, Hamernik RP: A Parametric Evaluation of the Equal Energy Hypothesis. In: Noise Induced Hearing Loss: Basic and Applied Aspects (eds. RJ Salvi, RP Hamernik, D Henderson, V Colletti), Plenum Press, 1986

Roberto M, Hamernik RP, Salvi RJ, Henderson D, Milone R: Impact Noise and the Equal Energy Hypothesis. J Acoust Soc Am 77:1514, 1985

Henderson D, Hamernik RP, Salvi RJ: A Parameter Evaluation of the Equal Energy Hypothesis. In: Noise Induced Hearing Loss: Basic and Applied Aspects, (eds. RJ Salvi, RP Hamernik, D Henderson, V Colletti), Plenum Press, 1985

Henderson D, Hamernik RP, Salvi RJ: Impulse Noise Repetition Rate: Implication for the Equal

Energy Hypothesis. J Acoust Soc Am 78, Supple 1-55, 1985

Henderson D, Hamernik RP: Assessing the Hazards of Impulse Noise Superimposed on Background Noise. J Acoust Soc Am 78:S5, 1985

Salvi RJ, Henderson D, Hamernik RP, Colletti V: Basic and Applied Aspects of Noise-Induced Hearing Loss. Plenum Press, NY, 1985

Henderson D, Salvi RJ, Pavek G, Hamernik RP: Amplitude Modulation Thresholds in Chinchillas with High-Frequency Hearing Loss. J of the Acoust Soc of Am 75:1177-1183, 1984

Hamernik RP, Turrentine G, Roberto M, Salvi RJ, Henderson D: Anatomical Correlates of Impulse Noise-Induced Mechanical Damage in the Cochlea. Hearing Research 13:229-247, 1984

Hamernik RP, Salvi R, Henderson D: Some Insights into Impulse Noise Trauma. Proc of the Nordic Acoustical Society - NAZ. 84, 13-15, June, Tronheim, Norway, pp 58-79, 1984

Henderson D, Salvi RJ, Hamernik RP, Ahroon WA: Neural Correlates of Sensorineural Hearing Loss. Ear and Hearing 4:115-129, 1983

Henderson D, Salvi RJ, Hamernik RP: Threshold, Temporal Resolution Frequency Selectively and Cochlear Pathology following Acoustic Trauma. 11th International Congress of Acoustic (Paris), 203-206, 1983

Slepecky N, Hamernik RP, Henderson D, Giraudi D, Coling D: Correlation of Audiometric Data with Changes in Cochlear Hair Cell Stereocilia Resulting from Impulse Noise Trauma. Acta Otolaryngology 93:329-340, 1982

Salvi RJ, Hamernik RP, Henderson D: Response Patterns of Auditory Nerve Fibers during Temporary Threshold Shift. Hearing Res 10:37-67, 1982

Giraudi D, Salvi RJ, Henderson D: Gap Detection in Hearing Impaired Chinchillas. J Acoust Soc Am 71:424-429

Salvi R, Ahroon WA, Perry J, Gunnarson A, Henderson D:Psychophysical and Evoked-Response Tuning Curves in the Chinchillas. Am J Otolaryngol 3:408-416, 1982

Salvi RJ, Henderson D, Hamernik RP: Animal Studies of Noise Induced Hearing Loss. Eighth National Noise Symposium, Dallas, TX, April 1982

Salvi RJ, Shaddock L, Ahroon WH, Henderson D: Changes in Evoked-Response Tuning Curves with Varying Levels of Hearing Loss. J Acoust Soc Am 71:S98, 1982

Salvi R, Ahroon WA, Henderson D: Evoked Response Tuning Curves in Normal and Hearing Impaired Chinchillas. Inner Ear Biology, Mainz, West Germany, September 5-8, 1982

Henderson D, Salvi R, Hamernik R: Is the Equal Energy Rule Applicable to Impact Noise? J of the Acoust Soc of Am Supplement 1, Vol 71, S50, 1982

Henderson D, Hamernik RP: Asymptotic Threshold Shift form Impulse Noise. In: New Perspectives in Noise Induced Hearing Loss, (eds. RP Hamernik, D Henderson RJ Salvi), Raven Press, NY, 1982

Salvi RJ, Perry J, Hamernik RP, Henderson D: Relationship Between Cochlear Pathology, VIII Nerve and Behavioral Responses after Acoustic Trauma. In: New Perspectives in Noise Induced Hearing Loss, (eds. RP Hamernik, D Henderson, RJ Salvi), Raven Press, NY, 1982

Henderson D, Salvi RJ, Hamernik RP: Neurological Basis for the Symptoms of Noise-Induced Hearing Loss. In: Personal Hearing Protection in Industry, (ed. PW Alberti), Raven Press, NY, 1982

Salvi RJ, Henderson D, Hamernik RP: Physiological Basis of Sensorineural Hearing Loss. In: Hearing Research and Theory, (eds. JV Tobias, ED Schubert), Academic Press, 1982

Henderson D, Hamernik RP, Salvi RJ, Ahroon W: Comparison of Auditory Evoked Response and Behavioral Thresholds in the Normal and Noise-Exposed Chinchilla. Audiology 22:172, 1982

Salvi RJ, Giraudi DM, Henderson D, Hamernik RP: Detection of Sinusoidally Amplitude Modulated Noise by the Chinchilla. J Acoust Soc Am 71(2):424-429, 1982

Slepecky N, Hamernik RP, Henderson D, Coling D: Correlation of Audiometric Data with Changes in Hair Stereocilia Resulting form Impulse Noise Trauma. Acta-Otolaryngol 93:329-340, 1982

Hamernik RP, Henderson D, Salvi RJ: New Perspectives on Noise-Induced Hearing Loss. Raven, Press, New York, NY, 1982

Henderson D, Salvi RJ, Hamernik RP, Pavek G: Effects of Hearing Loss on the Detection of Amplitude Modulated Noise. J Acoust Soc Am (A)69:S-104, 1981

Henderson D, Salvi RJ, Hamernik RP: Temporal Resolution and Noise Induced Hearing Loss. XVII Workshop on Inner Ear Biology, Montpelier, France, 1981

Hamernik RP, Henderson D, Salvi RJ: The Influence of Vibration on Asymptotic Threshold Shift Produced by Impulse Noise. Audiology 20:259-269, 1981

Salvi RJ, Hamernik RP, Henderson D: Correlations Among Cochlear Pathologies, Auditory Nerve Responses and Behavioral Responses Following Acoustic Trauma. XVII Workshop on Inner Ear Biology, Montpellier, France, 1981

Henderson D, Salvi RJ, Hamernik RP: Sensorineural Hearing Loss: New Insights for Physiology and Psychoacoustics. Am Speech and Hear Assoc, Los Angeles, CA, November, 1981

Slepecky N, Hamernik RP, Henderson D, Coling D: Ultra Structural Changes to the Cochlea Resulting form Impulse Noise. Arch Otorhinolargngol 230:273-278, 1981

Slepecky N, Hamernik RP, Henderson D: The Consistent Occurrence of a Striated Organelle (Friedmann Body) in the Inner Hair Cells of the Normal Chinchilla. Acta Otolaryngol 91:189-98

Henderson D, Salvi RJ, Hamernik RP: Neurophysiological Basis of TTS. Invited Paper J Acoust Soc Am (A)69:S-72, 1981

Henderson D, Hamernik RP, Salvi RJ: Lipoacusia da Rumure, Nozioni Antiche, Acquisizioni Ecenti e Nuove Propspetive. Symposium Intern. Recenti Acquisizioni Sullipoacusia da Rumore, Verona, Italy, Nov 24-25, 1980

Henderson D, Hamernik RP, Dosanjh DS, Mills JH: The Effects of Noise on Hearing - Critical Issues. Raven Press, New York, NY, 1976

Functional Correlates of Cochlear Injury

William W. Clark, Ph.D.
Central Institute for the Deaf
818 South Euclid
St. Louis, Missouri 63110

Program Area: *Noise-Induced Hearing Loss*
Grant Number: *2 R01 OH02128-06*
Start & End Dates: *09/01/84 - 05/31/93*
Funding Level: *$147,223 ($777,390 Cum)*

Importance to Occupational Safety and Health

The laboratory studies of noise-induced hearing loss in animal models and the relation with cochlear pathology directly address the long-term research goals described in the NIOSH prevention document. They will help to establish damage-risk criteria for human noise exposures, delineate the mechanisms of noise-induced hearing loss, determine the role of degenerative and recuperative processes, and determine the relative hazard of different schedules of noise exposure to help develop noise descriptors for workers exposed on an irregular basis. In addition, they will address the interaction between aging and noise-induced hearing loss.

Studies of otoacoustic emissions and acoustic intermodulation distortion products in an animal model with normal or damaged ears will help elucidate cochlear mechanisms and may lead to a better understanding of the basis of these tests as objective indicators of hearing function.

Objectives

The major goal of this project is to determine with behavioral and anatomical studies how the magnitude, pattern, and growth of hearing loss and structural damage are altered as the parameters of noise exposure are varied. Secondary objectives include evaluating hearing loss and cochlear damage as a function of age in a group of chinchillas that have never been exposed to noise and comparing the effects of noise exposure in young and old animals. In addition, acoustic measures of spontaneous otoacoustic emissions are being made from the ear canals of all subjects.

Methodology

Hearing thresholds are obtained by behavioral methods in chinchillas before, during, and after noise exposure; the ears of all animals are then prepared for microscopic evaluation of the cochlea. Acoustic measures are made with small probe microphones positioned in the ear canal of the unanesthetized animal.

Significant Findings

Some of the findings of the project include:

1. Asymptotic threshold shifts appear to set an upper bound on permanent threshold shifts. Animals exposed continuously for periods of up to 7 years have no more hearing loss during the seventh year of exposure than they had on the second day of the exposure. After exposure some recovery is observed, indicating a persisting temporary component to the hearing loss. Hearing loss in animals returned to noise after brief recovery periods show a much slower time course of development of threshold shift; these findings strongly suggest that surviving sensory cells are "toughened" by long-term exposure to noise and become more resistant to subsequent exposures.
2. Interrupting an exposure with rest is protective. Exposures with quiet periods interspersed produce less cochlear damage and less hearing loss than equal-energy continuous exposures. These data suggest that a 3-dB time-intensity tradeoff for equating hazardous effects of interrupted noise is overly protective; a 5-dB trading relation provides a better fit to the data.
3. Under some schedules of exposure, hearing sensitivity recovers even though the exposure continues. That is, some of the sensory elements of the inner ear can somehow "toughen" themselves against further insult by noise. For example, animals exposed to an octave band of noise centered at 4.0 kHz at 86 dB spl, 6 hours per day with 18 hours of quiet between exposures, or for 15 minutes per hour with 45 minute quiet periods between exposures, show initial hearing losses of 45 to 55 dB after the first few days. However, after one month of exposure on this schedule hearing losses of only 10 dB are observed, even though the longer exposure produces more cochlear damage than the shorter one.
4. The mechanism for the recovery phenomenon differs, depending upon the primary site of stimulation of the cochlea. High frequency, interrupted noise exposures (4.0 kHz obn, 86 dB spl, 15 minutes per hour for 72 days) show less recovery than equivalent low frequency exposures, suggesting different time constants for the recovery process.
5. Sensory cell damage from noise exposure precedes measurable hearing loss; individuals may sustain substantial cochlear damage before there is any measurable elevation of hearing sensitivity.
6. Chinchillas raised in a quiet environment for periods of up to 19 years show anatomical signs of age-related hearing loss (presbycusis), but the hearing ability of old chinchillas is not significantly worse than that of young animals. This is in stark contrast to the findings from humans, which show that 25% of Americans over 65 years of age have material impairment in hearing and suggest that much of what is typically called presbycusis in humans is caused by environmental factors, principally noise exposure.

Publications

Clark WW, Bohne BA, Reilly TJ: Effects of Periodic Rest on Hearing Loss and Cochlear Damage Following Interrupted Exposure to High-Frequency Noise. J Acoust Soc Am 84:S75-S76, 1988 (Abstract)

Clark WW, Solomonson M: Spontaneous Otacoustic Emission from a Chinchilla Ear Following Exposure to Noise. J Acoust Soc Am 82:S117A, 1987 (Abstract)

Clark WW, Bohl CD, Davidson LS, Melda KA: Evaluation of a Hearing Conservation Program at a Large Industrial Company. J Acoust Soc Am 82:S113,1987 (Abstract)

Bohne BA, Clark WW: Hazardous Effects of Noise on Hearing. Proc. International Conference on Noise Control Engineering, Vol II, pp 905-908, 1987

Sinex DG, Clark WW, Bohne BA: Effect of Periodic Rest on Physiological Measures of Auditory Sensitivity Following Exposure to Noise. J Acoust Soc Am 82:1265-1273, 1987

Clark WW, Bohne BA, Boettcher F: Effect of Periodic Rest on Hearing Loss and Cochlear Damage in the Chinchilla. J Acoust Soc Amer 84:1253-1264, 1987

Clark WW, Bohne BA: Attenuation and Protection Provided by Ossicular Removal. J Acoust Soc Amer 81:1093-1099, 1987

Bohne BA, Bozzay DG, Harding GW: Inter Aural Correlations in Normal and Traumatized Cochleas. J Acoust Soc Amer 80:1729-1736, 1986

Sinex DG, Havey DC: Neural Mechanisms of Tone-On-Tone Masking: Patterns of Discharge Rate and Discharge Synchrony Related to Rates of Spontaneous Discharge in the Chinchilla Auditory Nerve. J Neurophysiology 56:1763-1780, 1986

Clark WW, Bohne BA: Temporary Threshold Shifts from Attendance at a Rock Concert. J Acoust Soc Am 79, Supp 1, S48, 1986 (Abstract)

Clark WW, Bohne BA: Cochlear Damage: Audiometric Correlates, In: Sensorineural Hearing Loss, Mechanisms, Diagnosis, Treatment, (eds. E Harford, T Glattke), Univ of Iowa Press, pp 59-82, 1986

Clark WW: Spontaneous Otacoustic Emissions and Acoustic Intermodulation Distortion Products as Indicators of Hearing Loss and Cochlear Pathology. In: Sensorineural Hearing Loss: Mechanisms, Diagnosis, Treatment, (eds. E Harford, T Glattke), Univ of Iowa Press, pp 209-232, 1986

Clark WW, Bohne BA: The Effects of Noise on Hearing and the Ear. Resident and Staff Physician 31:6-19, 1985

Bohne BA, Marks JE, Glasgow GP: The Delayed Effects of Ionizing Radiation on the Ear. Laryngoscope 95:818-828, 1985

Bohne BA, Carr CD: Morphometric Analysis of Hair Cells in the Chinchilla Cochlea. J Acoust Soc Amer 77:153-158, 1985

Clark WW, Bohne BA: The Effects of Noise on Hearing and the Ear. Medical Times 112:17-22fm, 1984

Clark WW, Kim DO, Zurek PM, Bohne BA: Spontaneous Otacoustic Emissions in Chinchilla Ear Canals: Correlation with Histopathology and Suppression by External Tones. Hearing Research 16:299-315, 1984

Hearing Hazard Associated with Industrial Noise Exposure

Roger P. Hamernik, Ph.D.
Research Foundation of SUNY
107 Beaumont Hall
Plattsburgh, New York 12901

Program Area: *Noise-Induced Hearing Loss*
Grant Number: *2 R01 OH02317-06*
Start & End Dates: *08/01/84 - 07/31/93*
Funding Level: *$204,377 ($1,089,810 Cum)*

Importance to Occupational Safety and Health

Many industrial noise environments are characterized by high levels of impact noise that are superimposed on a continuous background noise, thus producing a very complex temporal signal. The limited demographic data and an increasing body of experimental data show that many of these "complex noise" environments pose an unusually high risk of hearing loss to the repeatedly exposed individual. The need exists to develop metrics which can be extracted from such "complex noise" environments and used to objectively estimate the hazards that such environments pose to hearing. Our research efforts are directed toward such a goal. Our experimental approach will yield a generalized methodology that can be used to model and evaluate all forms of industrial noise environments and holds the promise for producing analytical procedures that can be incorporated into a new generation of measurement equipment and used to gauge the hazards posed by virtually any industrial noise environment.

Objectives

There are three primary goals to the current research program: (1) to develop a model digital noise generation system which can be used to reproduce the essential characteristics of high-level, non-Gaussian industrial noise environments. The system will incorporate features such as multiple impact sources and room reflection characteristics to produce "complex" noises whose "Gaussian" and "non-Gaussian" components can be controlled; (2) to explore the applicability of new approaches to signal analysis, such as, adaptive noise cancellation, frequency domain kurtosis, and cepstral analysis to quantitatively evaluate non-Gaussian noise environments for the purpose of hearing

conservation; (3) to expose experimental animals (chinchillas) to "complex noise" paradigms that are designed to explore which metrics of a "complex noise" environment are suitable predictors of the hazard to hearing following prolonged exposures. The noise exposures are being designed to test the hypothesis that a high kurtosis noise is more hazardous to hearing than is a low kurtosis exposure of the same amplitude spectrum and total energy, and that this effect is frequency specific.

Methodology

An approach to digital noise generation has been developed which is capable of producing noise whose statistical properties and amplitude spectrum are under experimental control. The basic idea is that the desired noise is designed in the frequency domain by manipulations of the phase spectrum. In essence, once an amplitude spectrum is chosen, phase spectrum manipulations can produce peaks in a continuous noise which derive their energy from any selected portions of the amplitude spectrum. Preliminary results indicate that entire families of noises having the same spectrum but continually varying statistical properties can be created. Noise environments similar to bottling, stamping, punchpress operation, etc. can be modeled. Analytical methods using adaptive noise cancellation are being developed to decompose the complex noise into Gaussian and non-Gaussian components, and complex cepstral analysis and frequency domain kurtosis procedures are being explored as methods for extracting quantitative information from the non-Gaussian component of the noise. The animal experiments being conducted use a standard paradigm. Chinchillas are being exposed for five continuous days to various non-Gaussian noise paradigms. Hearing thresholds are obtained prior to exposure and at regular intervals following exposure using brainstem evoked potentials. Sensory cell populations are obtained from each animal, and relations between noise parameters, audiometry, and histology are derived.

Significant Findings

1. A digital noise generation system which relies upon manipulations of the phase spectrum can be successfully used to produce noise exposure stimuli of constant energy, fixed spectrum, and a variable kurtosis. The system which is designed to generate non-Gaussian signals in "real time" can effectively simulate a wide variety of complex industrial noise environments.
2. Preliminary experiments using the above system to generate relatively low levels (90 and 95 dB SPL rms) of noise have shown that there are statistically significant differences in either permanent threshold shifts or sensory cell loss for Gaussian and non-Gaussian continuous noise exposures of the same total energy and spectrum. For each of the two levels studied, the high kurtosis exposures produced the greater loss.
3. On the basis of our earlier results, as well as those summarized above, new methods for the analysis of complex industrial noise environments need to be developed in order to evaluate such environments for their potential to cause hearing loss.

Publications

Hsueh KD, Hamernik RP: Performance Characteristics of a Phase Domain Approach to Random Noise Synthesis. J Noise Control Engineering, in press, 1991

Davis IR, Hamernik RP, Turrentine G, Ahroon WA: Frequency Selectivity in Noise-Exposed Chinchillas. JASA 88:S19(A), 1990

Hsueh KD, Hamernik RP: Performance Characteristics of a Phase Domain Approach to Random Noise Synthesis. J of Noise Control Engineering, in press, 1990

Hamernik RP, Ahroon WA, Davis RI, Axelsson A: Noise and Vibration Interactions: Effects on Hearing. J Acoust Soc Am 86:2129-2137, 1989

Hamernik RP, Turrentine GA, Ahroon WA, Patterson JH: The Quantitative Relation between Sensory Cell Loss and Hearing Thresholds. Hear Res 38:199-212, 1989

Davis RI, Ahroon WA, Hamernik RP: The Relation among Hearing Loss, Sensory Cell Loss, and Tuning Characteristics in the Chinchilla. Hear Res 41:1-14, 1989

Hsueh KD, Hamernik RP: A Generalized Approach to Random Noise Synthesis. J Acoust Soc Am 85:S40(A), 1989

Hsueh KD, Hamernik, RP: A Generalized Approach to Random Noise Synthesis: Theory and Computer Simulation. J Acoust Soc Am 87:1207-1217, 1989

Hamernik RP, Hsueh KD, Ahroon WA, et al.: Kurtosis Measurements: Implications for Noise Exposure Criteria. J Acoust Soc Am 86:S72(A), 1989

Hsueh KD, Hamernik RP: A Generalized Approach to Random Noise Synthesis: Hardware Implementation and Performance Characteristics. J Acoust Soc Am 86:S22(A), 1989

Hamernik RP, Ahroon WA, Patterson JH: Threshold Recovery Functions Following Impulse Noise Trauma. J Acoust Soc Am 84:941-950, 1988

Hamernik RP, Roberto M, Ahroon WA, Davis RI: The Interaction of Impulse Noise and Continuous Noise: Energy and Spectral Considerations in the Production of Hearing Loss. Proc 5th Int'l Congress on Noise as a Public Health Problem. Stockholm, Sweden August 21-25, 1988. Also, J Acoust Soc Am 81:S76(A), 1988

Hamernik RP, Ahroon WA, Davis RI: The Influence of Whole-Body Vibration on Noise-Induced Hearing Loss: A Review of Animal Experiments. In Recent Advances in Research on the Combined Effects of Environmental Factors, (ed. O Manninen), Pk Paino Oy, Tampere, Finland, 1988. Also, J Acoust Soc Am 83:S21(A), 1988

Davis RI, Ahroon WA, Hamernik RP: Changes in Frequency Selectivity in the Chinchilla Following a Noise-Induced Permanent Thresholds Shift. J Acoust Soc Am 83:S116(A), 1988

Hamernik RP, Ahroon WA, Davis RI: The Effect of Combinations of Noise and Whole Body Vibration on Hearing Thresholds in the Chinchilla. Proceedings 3rd Int'l Conference on the Combined Effects of Environmental Factors, Tampere, Finland. August 15-18, 1988

Hamernik, RP, Henderson D, Salvi RJ: The Interaction Between Continuous and Impulse Noise: Frequency Effects. Proc Recent Advances in Research on the Combined Effects of Environmental Factors (eds. A Okada, O Manninen), Kyoei Co. Ltd, Kanazawa, Japan, 1987

Hamernik RP, Ahroon WA, Patterson JH: Threshold Recovery Functions Following Impulse Noise Trauma. J Accoust Soc Am 82,S26(A), 1987

Hamernik RP, Patterson JH, Turrentine G: The Quantitative Relation Between Sensory Cell Loss and Hearing Thresholds. Proceeding VIIIth Symposium Cochlear Research, Halle, DDR, and 11th Midwinter Meeting of the Association for Research in Otolaryngol, Tampa, Florida, 1987

Effect of Industrial Work-Related Variables on Achieved Hearing Protector Attenuation

John G. Casali, Ph.D.
Virginia Polytechnic Institute and State University
Department of ISE
Blacksburg, Virginia 24061-0118

Program Area: *Noise-Induced Hearing Loss*
Grant Number: *5 R01 OH02540-02*
Start & End Dates: *05/16/88 – 08/15/90*
Funding Level: *$55,757 ($107,502 Cum)*

Importance to Occupational Safety and Health

For the worker exposed to hazardous levels of industrial noise, personal hearing protection devices (HPDs) are commonly used in defense against noise-induced hearing loss. It is estimated that over nine million American workers are exposed to daily average occupational noise levels above the 85-dBA time weighted average level at which OSHA requires HPDs to be supplied. The success of many industrial hearing conservation programs is dependent upon the performance of HPDs and the practical industrial need is to have an accurate and reasonable estimate of the attenuation to be reliably obtained under workplace conditions. This research project was aimed at determining the effects of various work-related influences on hearing protector attenuation, with the objective of providing empirical data which reflect workplace performance, not optimal laboratory performance, of the devices.

Objectives

This two-year project entailed a laboratory attenuation study during the first year and a determination of on-the-job attenuation for industrial subjects in the second year. As a secondary initiative, user HPD comfort and acceptability data were obtained in the laboratory and again in-field. The fundamental objective of the laboratory simulation study was to determine if several "real-world" influences and different HPD fitting procedures could be reproduced in the confines of the laboratory and the magnitude of

their effect on spectral attenuation loss with several common HPDs measured. Three HPDs common to those investigated in the laboratory study were also used in-field so that comparisons on common devices could be performed. In essence, the in-field validation phase was designed to ascertain if workplace influences modeled in the laboratory could yield an accurate assessment of an HPD's protection performance that will be provided in the industrial setting.

Methodology

In the first-year laboratory study, a complete factorial experimental design was applied to assess the independent variables of HPD-type (premolded, multi-flange polymer earplug, user-molded foam earplug, foam cushion earmuff, and earmuff over foam earplug combination), movement activity, wearing time, and HPD fitting procedure on the dependent measures of attenuation in dB and self-report ratings. To provide a comparison against the usual laboratory test conditions of a seated, motionless subject wearing properly-fit HPDs for a short testing period, this study presented the potential real-world effectors of movement activity, subject fitting of the device, and prolonged wearing periods. All attenuation measurements were obtained in a sound field using Békésy computer-controlled audiometry, with occluded (HPD on) and unoccluded (open ear) thresholds determined at nine 1/3-octave test bands centered at 125 to 8000 Hz. Subjects consisted of 40 normal hearing, non-users of HPDs. Each subject attended four experimental sessions following screening and was assigned one HPD. In the first two sessions, subjects initially fit the HPD according to a "subject-fit" condition in which only manufacturer's package instructions were presented. In the last two sessions, subjects initially fit the HPD according to a "trained-fit" condition to achieve proper fit. In both fitting conditions, subjects ultimately fitted the devices on themselves, after which no further protector adjustments were allowed. After the initial fit of the device, attenuation was measured. Then subjects proceeded through a two-hour wearing period in which attenuation measurements were obtained after one hour and again after two hours. The wearing periods consisted of either highly kinematic work activity using a BTE Work Simulator or vigorous temporomandibular movement.

For the second-year study, each of the 40 industrial workers were supplied with one of four HPDs (multi-flange polymer earplug, foam earplug, foam cushion earmuff, or rubber pod canal cap) to use while working. Workers received the HPDs with only the manufacturer's instructions as a guide to use. Workers used the HPDs for one month, during which on three occasions they were pulled (unannounced) from their work at random intervals and attenuation-tested. At the end of this month, workers received more detailed training on proper fitting through an interactive session with the experimenter and then returned to the workplace to use the devices for a second month. Attenuation tests were conducted, unannounced, at similar intervals to those used during the first month. Thus, actual industrial protection levels were obtained using an experimental design which was exactly balanced to that of the first-year laboratory study, with three common HPDs, common fitting procedures, and identical sound field test conditions.

Significant Findings

1. When subjects fit earplugs using only the manufacturers' on-package instructions, protection levels at 1000 Hz and below were significantly lower (by 4 to 14 dB) than those obtained when the subject was trained in proper fitting. Attenuation afforded by the foam plug, which requires considerable manipulation, was most susceptible to the fitting procedure effects in both studies. The earmuff, which was straightforward to don, and the canal cap each showed no differences due to fitting procedure.
2. In the laboratory protocol, after the two-hour activity period, protection levels afforded by the premolded earplug decreased by up to 6 dB compared to the pre-task levels. The earmuff also exhibited a small drop in attenuation due to the activity movements, but the foam plug, which was stable in the ear canal once seated, did not.
3. Based on the previous two findings, there is considerable evidence that with poor protector fit and/or during vigorous wearer activity, the risk of compromised hearing protection and OSHA noncompliance increases. On average across the four devices tested, the actual field Noise Reduction Ratings (NRRs) were less than one-half of the labeled NRRs. The differences were smallest for the earmuff.
4. The post-task laboratory results, which were closest to those from the industrial workplace both in accuracy and conditions obtained under, were still disappointing in their correspondence with actual protection levels except for the earmuff. These findings collectively indicate the inappropriateness of using laboratory-derived attenuation ratings for estimation of the protection levels actually afforded by certain insert protectors in the dynamic workplace.

5. Predictions of the broadband NRR for a single worker from single-frequency data were reasonably accurate using 500 or 1000 Hz.
6. Standard laboratory protocols (e.g., ANSI S3.19-1974; ANSI S12.6-1984) for measuring hearing protector attenuation require revision if realistic influences on protection levels are to be accounted for in labeled Noise Reduction Ratings.

Publications

Casali JG, Park MY: Effects of Dynamic Work Conditions and Wearer Fit on Attenuation of Slow-Recovery Foam Earplugs. Journal of Sound and Vibration, in press, 1990

Park MY, Casali JG: An Empirical Study of Comfort Afforded by Various Hearing Protection Devices: Laboratory Versus Field Results. Applied Acoustics, in press, 1990

Park MY, Casali JG: A Controlled Investigation of In-Field Attenuation Performance of Selected Insert, Earmuff, and Canal Cap Hearing Protectors. Human Factors, in press, 1990

Casali JG, Park MY: Attenuation Performance of Four Hearing Protectors Under Dynamic Movement and Alternative User Fitting Conditions. Human Factors 32(1):9-25, 1990

Park MY, Casali JG: Hearing Protector Attenuation Performance Under Different Simulated Work and Fitting Conditions. Journal of the Acoustical Society of America Suppl 1, Vol 87, S24, 1990

Park MY, Casali JG: A Laboratory Simulation of Selected In-field Influences on Hearing Protector Performance. Proc of the 1989 Human Factors Society 33rd Annual Conference, Denver, CO, 946-950, Oct 16-20, 1989

Casali JG, Grenell JF: An Exploratory Study of Moderate Physical Activity and Selected Design Attribute Effects on Earmuff Attenuation. American Industrial Hygiene Association Journal 50(9):480-485, 1989

I.D. and Evaluation of Noise in Vocational Education Laboratories

Glen M. Miller, Ed.D.
The University of Arizona
College of Agriculture
Department of Agricultural Education
Forbes 226
Tucson, Arizona 85721

Program Area: *Noise-Induced Hearing Loss*
Grant Number: *5 R03 OH02671-02*
Start & End Dates: *09/30/89 – 09/29/91*
Funding Level: *$21,615 ($39,861 Cum)*

Importance to Occupational Safety and Health

Vocational education laboratories such as Trade and Industrial Education, Industrial Arts Education, and Agricultural Education are equipped with tools and machinery which duplicate those used in the industry which students are being prepared to enter.

The majority of vocational educators do not recognize the risk which noise poses to their students or themselves. Teachers lack basic information about the exposure levels they and their students experience in their instructional laboratories. In order to fill this informational vacuum and to prevent risk from noise exposure to vocational education students and instructors, the following objectives will be addressed:

Objectives

1. To survey and develop an inventory of the power tools and equipment found in selected vocational education laboratories in Maricopa and Pima Counties, Arizona.
2. To measure the noise level in dB(A) of common power tools and equipment used in selected vocational education laboratories in Maricopa and Pima counties, Arizona.
3. To document the characteristics of the selected facilities which could have an impact on noise levels.
4. To measure student and teacher percent dose for daily and 40-hour equivalent values, based on 3 and 5-dB exchange rates, in each facility's environment.
5. To disseminate findings and recommendations to vocational educators and administrators of vocational education programs by all available means.

Methodology

This study will be conducted as descriptive research with survey data collected on-site by researchers. The accessible population includes all students enrolled and teachers of programs in the areas of Trade and Industrial Education, Industrial Arts Education, and Agricultural Education at the secondary level in the state of Arizona. Approximately 38,547 students were enrolled in their programs in 1987 in Arizona.

The target population will include secondary students enrolled in Vocational Agriculture, Trade and Industrial Education, and Industrial Arts in Pima and Maricopa Counties where welding is specified as a part of the curriculum or the major emphasis of the course. Pima and Maricopa Counties contain 75% of the population of the state of Arizona.

From the 54 programs in Pima and Maricopa Counties offering welding, a proportional stratified random sample consisting of 50% of the programs (27) will be assigned to strata based upon type of facility. All 54 programs in Maricopa and Pima Counties will be surveyed by mailed questionnaire to determine the type of construction and acoustical treatments of the facility. The 27 selected programs will be assigned proportionally to the appropriate facility type.

Four students and the teacher will be randomly assigned to wear a dosimeter and data storage unit. Random assignment of students to dosimeters will reduce variability among students in welding and grinding techniques.

Data collected will be reported as frequencies, means, and modes. Data collected will be daily and 40-hour equivalent values, based upon 3 and 5-dB exchange rates, for teachers and students. Correlations will be calculated between the above factors and the strata of facility type.

The acoustical characteristics of each facility will be evaluated by determining reverberation time (RT60). Dimensional measurements will be taken and materials of construction will be noted. Any noise attenuating features will be noted such as insulation, ceiling tile, etc.

Significant Findings

The findings below are preliminary and no conclusions about significance can be made at this time. Trends are emerging which would indicate that this study will lead to very significant findings.

Preliminary RT60 Values by School Laboratory and Characteristics:

Sch #	RT60 Value	Walls;Ceilings;Floor;Partition
1	1.16	Brick/Glass; Wood; Concrete; None
3	.77	Plastic backed insulation; Plastic backed insulation; Concrete; Wood Panel
4	.72	Metal Panel; Insulated board; Concrete; None
5	1.59	Bricks; Sheetrock; Concrete; None
7	2.09	Concrete block; Steel; Concrete; Block
8	.73	Brick; Acoustical Tile; Concrete; Block/Steel

The following sound levels in decibels were recorded for particular types of equipment (school number in parentheses):

portable power saw - 108.4 (1), 95.7 (3)
radial arm saw - 110.9 (1), 101.4 (4), 110.0 (5)
abrasive cut-off saw - 100.8 (1), 93.1 (2), 100.2 (6), 100.5 (7)
pedestal grinder - 90.1 (1), 90.0 (2), 92.6 (3), 89.0 (5), 96.7 (7), 90.3 (8)
router - 90.5 (1), 91.0 (3)
arc welding (lab center) - 91.7 (1), 87.5 (2), 89.0 (3), 86.7 (4)
large angle grinder - 97.6 (2), 110.1 (6), 98.6 (7), 97.4 (8)
forge - 98.9 (2), 97.3 (4)
table saw - 87.1 (3)
small angle grinder - 97.7 (3), 102.1 (5)
belt sander - 96.9 (3)

Data from one student at one school for fifteen minutes of arc welding were: Measured Dose = 17.2, Proj. Dose = 528.0, Single Event Level (SEL) = 127.2 dB, Level (LVL) = 97.4 dB, Time = 15.36 min., Level minimum (Lmin) = 71.5 dB, Level maximum (Lmax) = 116.0 dB, Level peak (Lpk) = 140.5 dB.

Several non-noise safety factors were examined with respect to compliance with OSHA standards in schools 1, 3, 4, 6, and 7. The numbers in parentheses after the factors indicate the maximum possible scores; the five numbers for each factor are the individual school scores, respectively.

Walking-working surface (100.9): 66.14, 91.24, 91.24, 58.96, 61.14
Means of egress (40.82): 18.37, 37.73, 9.28, 18.37, 25.82

Fire protection (79.91): 79.91, 53.64, 44.00, 34.45, 44.00
Medical first aid (26.91): 0, 8.55, 26.91, 0, 0
Personal protective equipment (39.26): 29.62, 29.46, 19.82, 9.82, 29.46
Tools (193.57): 94.11, 121.01, 111.57, 65.37, 128.74
Welding, cutting, and brazing (94.92): 57.65, 57.19, 85.19, 85.28, 86.01
Electrical (67.37): 38.82, 48.82, 67.37, 57.73, 57.73
Compressed air equipment (35.09): 0, 26.82, 35.09, 0, 26.36
Envir. control (111.29): 73.56, 83.56, 92.01, 54.28, 73.56

Safety Score Total (792.23): 431.91, 558.10, 582.26, 325.30, 532.82

Percentage Compliance (100%): 54.5%, 70.4%, 74.0%, 41.0%, 67.3%

Symposium: Noise-Induced Hearing Loss

Donald Henderson, Ph.D.
State University of New York at Buffalo
Parker Hall, Room 105
Buffalo, New York 14260

Program Area: *Noise-Induced Hearing Loss*
Grant Number: *1 R13 DC00007-01*
Start & End Dates: *05/01/90 - 04/31/91*
Funding Level: *$10,000 ($10,000 Cum)*

Importance to Occupational Safety and Health

The proposed conference is designed to integrate the current state of knowledge on the biological bases and applied aspects of noise-induced hearing loss. In the past five years, scientists have made considerable progress in understanding the active processes in the cochlea and the cell biology and biochemistry of hair cells. Advances have also been made in understanding the parametric relation between acoustic variables and hearing loss and how the effects of noise can be influenced by other non-acoustic variables (particularly impulse/impact noise). In addition, engineers have developed devices that more accurately capture the "noise dose" under a wide range of exposure conditions. Progress has also been made in the design of hearing protection devices. For society to use the new information and for scientists to continue to make progress, it is important to provide a forum to integrate results across disciplines and provide insights for future research. The proposed conference will bring together experts from most of the disciplines interested in noise-induced hearing loss. Each participant will present a critical review of a topic along with their most recent findings. To disseminate this information to an even broader audience, the papers and discussions will be edited and published.

Immunotoxicology of Phenols on Epidermal Immune Cells

James J. Nordlund, M.D.
University of Cincinnati
College of Medicine
Department of Dermatology
231 Bethesda Avenue, ML #592
Cincinnati, Ohio 54267-0592

Program Area: *Dermatological Conditions*
Grant Number: *3 R01 OH02091-05S1*
Start & End Dates: *08/01/87 – 01/31/91*
Funding Level: *$200,517 ($479,138 Cum)*

Importance to Occupational Safety and Health

Cutaneous disorders are one of the most common occupationally related problems. Although they rarely cause death, they are responsible for significant morbidity, i.e., loss of time from work, discomfort, and secondary infections. Most occupational skin disorders are considered a form of contact dermatitis. Contact dermatitis is subclassified into two categories, allergic (immunologically mediated) and irritant. Numerous epidemics and individual episodes of occupationally related skin disorders have been carefully evaluated to determine the offending chemical(s) and the pathogenesis (immune or irritant mediated). Occasionally these investigations are successful. More commonly, no specific chemical(s) can be identified as the inciting agent(s).

Since the 1930's it has been well documented that antioxidants like monobenzone or paratert butylcatechol cause leukoderma, i.e., a loss of melanocytes from the epidermis. Not all subjects, however, exposed to these agents, even in very high concentrations such as 40% creams for periods of up to two years, develop leukoderma. This suggests two conclusions: (1) that individuals have different susceptibility to the injurious effects of antioxidants; and (2) that these compounds are not simple toxins for pigment cells.

Antioxidants like butylated hydroxytoluene and monomethyl ether of hydroquinone (4-hydroxyanisole) are ubiquitous chemicals, similar in their structure to the known leukodermic agents. They are present in virtually all foods, medicinal creams, and many occupational and daily settings. We have studied the effects of monobenzone, paratert butylcatechol, butylated hydroxytoluene, and monomethyl ether of hydroquinone applied to skin of mice. We found that these agents can alter the number of cells expressing class II antigens. Some of the animals exhibit *in vivo* hyperreactivity to subsequent exposure to known allergens like DNCB. These compounds also increase the expression of Thy-1+ molecules and the number of Thy-1+ dendritic epidermal cells, a group of lymphocytes which are thought to be T-suppressor cells. However, the immune responsiveness of animals with increased amounts of Thy-1 cells to subsequent exposure to known allergens is not simply dependent on the morphologic changes nor simply on the ratio or quantity of Ia (activator) to Thy-1+ (suppressor) cells. Results of both *in vivo* and *in vitro* studies show that the immune/inflammatory responsiveness of epidermal cells of animals exposed to antioxidants is altered but in an intricate and complex manner. We conclude that antioxidants which are ubiquitous in our daily lives are not biologically inert, but rather alter the function of the skin in subtle ways. Subsequent exposure to other chemicals and environmental agents like sunlight produces inflammatory responses different from those that would be observed in skin not predisposed by exposure to these chemicals. We propose that some of the mysteries of some occupationally-related cutaneous problems will be resolved by studying the effects *in vitro* and *in vivo* of these common antioxidants on epidermal cells.

Objectives

Our major hypothesis is that antioxidants are not inert, but rather alter the inflammatory/immune responsiveness of the skin. Two cytokines produced by various cells of the skin are thought to be initiator signals for inflammation, specifically interferon-γ (IFN-γ) and IL-1. A third cytokine, α-MSH, seems to be a potent and natural antagonist (suppressor) of some interferon and IL-1 mediated activities. A fourth cytokine is a traffic signal, the intercellular adhesion molecule (ICAM), and it is needed to attract and retain inflammatory cells within the epidermis. We suggest that these four molecules compose at least part of a self-regulating immune/inflammatory system within the skin. We propose to study the effects of antioxidants on the initiator, suppressor, and trafficking molecules.

Methodology

We are using two strains of mice, the C57BL/6 and its congenic mutant C57BL/Ler-vit/vit mouse. The latter mouse exhibits all the features of an animal highly susceptive to antioxidants. It exhibits

leukoderma and altered epidermal immune reactivity. We are studying the effects of antioxidants on the function of Langerhans cells, lymphocytes, melanocytes, and keratinocytes *in vitro* and *in vivo* from these animals on the expression of the initiator suppressor signals. We are using immunofluorescence, immunoelectron microscopy, molecular probes, as well as *in vitro* functional assays such as mixed epidermal lymphocyte reactions.

Significant Findings

We have documented with a high degree of probability that α-MSH is synthesized within the epidermis. The source at least of MSH seems to be either the melanocyte and/or Thy-1 lymphocyte. In addition, melanotropic agents and melanocytes seem to be essential components of the immune/inflammatory regulatory loop. Loss of melanocytes is accompanied by loss of inflammatory responsiveness. α-MSH is a potent melanotropic stimulant and an immune suppressant. α-MSH blocks both the afferent and efferent cutaneous immune responsiveness which can be reversed by simultaneous administration of interleukin-1. It should be noted that antioxidants markedly increase the production of IL-1 *in vitro* and probably MSH expression as well. The effects of antioxidants on interferon-γ and ICAM are under study.

We have also documented that IL-1, IL-6, TNF-α, and IFN-γ all alter melanocyte function. Our final goal is to understand how these four biological modifier molecules interact and how that is altered by ubiquitous antioxidants. We will use the information for these studies in an attempt to understand better occupationally-related skin disease.

Publications

Rheins LA, Moravec RA, Nordlund ML, Trinkle LS, Nordlund JJ: The Role of Antioxidants in Skin Immune Reactions: The Use of Flow Cytometry to Determine Alterations in Ia Positive Epidermal Cells in Allergic Contact Dermatitis. J Cosmet Sci 40:101-107, 1989

Swope VB, Abdel-Malek ZA, Sauder DN, Nordlund JJ: A New Role for Epidermal Cell–Derived Thymocyte Activating Factor (ETAF)/IL-1 as an Antagonist for Distinct Epidermal Cell Function. J Immunol 142:1943-1949, 1989

Rheins LA, Cotleur AL, Kleier RS, Hoppenjans WB, Sauder DN, Nordlund JJ: Alpha-melanocyte Stimulating Hormone Modulates Contact Hypersensitivity Responsiveness in C57BL/6 Mice. J Immunol, in press, 1989

Nordlund JJ, Amornsiripanitch S, Rheins LA, Abdel-Malek ZA, Boissy RE, Bell M: Role of the Melanocyte in Epidermal Inflammatory and Immune Responses. Pigment Cell Res Suppl 1:101-112, 1988

Abdel-Malek ZA, Swope VB, Trinkle LS, Ferroni EN, Boissy Re, Nordlund JJ: Alteration of the Cloudman Melanoma Cell Cycle by Prostaglandins E_1 and E_2 Determined by Using a Bromodeoxyuridine Method of DNA Analysis. J Cell Physiol 136:247-256, 1988

Nordlund JJ, Abdel-Malek ZA: Mechanisms for Post-Iinflammatory Hyperpigmentation and Hypopigmentation. In: Advances in Pigment Cells Research. (ed. J Bagnara) New York, NY, 219-236, 1988

Nordlund JJ: Postinflammatory Hyperpigmentation. Dermatol Clinics 6:186-192, 1988

Amornsiripanitch S: Immune Studies in the Depigmenting C57BL/Ler-vit/vit mice. J Immunol, 140:3438-3445, 1988

Rheins LA, Young EM, Nordlund ML, Berning RB, Amornsiripanitch N, Nordlund JJ: Rapid Induction of Thy-1 Antigenic Markers on Keratinocytes and Epidermal Immune Cells in the Skin of Mice Following Topical Treatment With Common Preservatives Used in Topical Medications and in Foods. J Invest Dermatol 89:495, 1987

Rheins LA, Collins CE, et al: Suppression of the Cutaneous Immune Response Following Topical Application of the Prostaglandin PGE_2. Cell Immunol 106:33, 1987

Rheins LA, Young EM, et al: Rapid Induction of Thyl Antigenic Markes on Keratinocytes and Epidermal Immune Cells in the Skin of Mice Following Topical Treatment With Common Perservatives Used in Topical Medications and Food. J Invest Dermatol 89:495, 1987

Rheins LA, Nordlund JJ: Modulation of the Population Density of Epidermal Langerhans Cells: A Method to Enhance or Suppress Cutaneous Immune Reactivity. J Immunol 136:867, 1986

Rheins LA, Palkowski MR, Nordlund JJ: Alterations in Cutaneous Immune Reactivity to

Dinitrofluorobenzene in Graying C57BL/vi•vi mice. J Invest Dermatol 86:539–42, 1986

Nordlund JJ, Forget B, Kirkwood J, Lerner AB: Dermatitis Produced by Applications of Monobenzone in Patients with Active Vitiligo. Arch Dermatol 121:1141–1145, 1985

Nordlund JJ, Ackles AE: Melanocytotoxins and Fatty Acids which Stimulate Proliferation of Melanocytes in Murine Pinnal Epidermis: A Possible Role for Arachidonic Acid Metabolism in Regulation of Melanocyte Growth. In: Pigment Cell, 1985: Biological, Molecular, and Clinical Aspects of Pigmentation, (eds. J Bagnara, SN Klaus, E Paul, M Schartl, University of Tokyo Press, Tokyo, Japan, 1985

Biological Monitoring for Exposure to Coal Tar

Regina M. Santella, Ph.D.
Columbia University
Division of Environmental Science
650 West 168th Street
New York, New York 10032

Program Area: *Dermatological Conditions*
Grant Number: *5 R01 OH02622-02*
Start & End Dates: *01/01/89 - 12/31/91*
Funding Level: *$425,400 ($215,550 Cum)*

Importance to Occupational Safety and Health

A major goal of biological monitoring for exposure to genotoxic agents is to identify occupations as well as individuals at elevated risk for cancer development. Methods for the detection of carcinogen-DNA and protein adducts have been developed. These methods require the collection of blood or tissue samples and are not practical for routine occupational monitoring. In this proposal, methods will be developed for the determination of exposure to benzo(a)pyrene (BP) by measurement of BP and its metabolites in urine. Urine is much more readily collected than blood, and this method should thus simplify workplace screening.

Objectives

The major objective of this work is the development of a new technique to monitor human exposure to BP, a polycyclic aromatic hydrocarbon (PAH), by measurement of urinary excretion. An immunoassay for measurement of BP and its metabolites in urine will be developed utilizing monoclonal antibodies recognizing these compounds. This new assay will be validated in a model population, crude coal tar treated psoriasis patients, and controls. Blood and urine will be collected from patients and controls. Exposure to BP will be measured by a panel of previously developed assays, including quantitation of white blood cell DNA adducts by immunoassay and ^{32}P postlabeling, measurement of albumin adducts by immunoassay, and measurement of serum antibodies to BP-DNA adducts by immunoassay. Urines will be analyzed for excreted mutagens with the Salmonella typhimurium assay, for excretion of 1-hydroxypyrene by an HPLC method with fluorescence detection, and with the new immunoassay to be developed in this proposal. The levels of different biological markers will be correlated with exposure.

Methodology

To develop an immunoassay for the measurement of BP and its metabolites in urine, monoclonal antibodies have been developed from animals immunized with BP covalently coupled to carrier protein. These antibodies were characterized in terms of sensitivity and specificity by competitive enzyme-linked immunosorbent assay (ELISA). An ELISA has been developed for the sensitive detection of BP and a number of its metabolites in urine. To validate the ELISA, mice were treated with radiolabeled BP and urine was collected. Metabolites were measured by the ELISA and values compared to those determined by radioactivity.

Blood and urine is being collected from 40-50 crude coal tar treated psoriasis patients and controls. Blood is separated into plasma, white blood cell, and red blood cell fractions and frozen. DNA is being isolated from the white blood cells and adducts determined by ELISA utilizing previously developed antibodies against BP diol epoxide modified DNA. These antibodies recognize a number of structurally related PAH diol epoxide adducts and thus provide a general marker of exposure to this class of chemicals. Total hydrophobic adducts are being quantitated with the ^{32}P postlabeling assay. BP protein adducts are being measured in an ELISA with an antibody recognizing these adducts. Plasma will be tested for the presence of antibodies to BP-DNA adducts by noncompetitive ELISA as an alternate marker of exposure to BP.

In addition to quantitation of urinary levels of BP and its metabolites by ELISA, 1-hydroxypyrene is being measured by HPLC and mutagens in urine are being determined with the Salmonella typhimurium mutagenesis assay. Results from the different biological assays will be correlated with exposure.

In a small subset of patients, skin biopsies were obtained at the time of treatment. PAH-DNA adducts were visualized in frozen sections by immunohistochemical staining with adduct specific antibody followed by fluorescent labeled secondary antiserum. This allowed visualization of adducts in specific cell types. Adducts were also quantitated on DNA isolated from the biopsies by ^{32}P postlabeling.

Significant Findings

Monoclonal antibodies have been developed against BP and its metabolites from the spleen cells of animals immunized with BP covalently coupled to carrier protein. These antibodies were characterized in terms of sensitivity and specificity by competitive ELISA. The ELISA has a 50% inhibition of antibody binding at 4 pmole of BP/well. There is also significant crossreactivity with a number of BP metabolites including 1-, 3-, 4-, 5-, and 11-hyroxy-BP, 7,8- and 9,10-BP diols and 7,8,9,10-BP tetrol. Several other PAHs, including pyrene, 1-OH-pyrene, 1-aminopyrene and 1-nitropyrene, crossreact with the antibody. An ELISA was developed for the sensitive detection of BP and a number of its metabolites in urine. To validate the ELISA, mice were treated with radiolabeled BP and urine was collected. After treatment with beta glucuronidase and aryl sulfatase, metabolites were isolated by several different chromatography procedures. These included extraction with ethyl acetate, chromatography on Sep-pak C18 cartridges, chromatography on an Amberlight XAD2 column and immunoaffinity chromatography with the monoclonal antibodies. Sep-pak and immunoaffinity chromatography gave the highest recovery of metabolites. Isolated metabolites were counted for radioactivity and analyzed by competitive ELISA. The values by ELISA, determined with a standard curve of BP, were about one-third those determined by radioactivity. Although unmetabolized BP is not excreted in the urine, it is used as the standard since the metabolite ratio in the urine, especially in humans, is unknown. Thus, the assay will provide a relative measure of metabolites present.

An immunofluorescence method has been developed for the localization of adducts in skin biopsies. Staining with the PAH-DNA adduct specific antiserum followed by fluorescein-labeled secondary antiserum indicated specific nuclear staining in biopsies of coal tar treated patients. Biopsies from untreated controls were negative. Adducts were also measured by ^{32}P postlabeling of DNA isolated from the biopsies. Multiple hydrophobic adducts were seen in all biopsies of patients but not in controls. The immunohistochemical method should be applicable to the detection of adducts in biopsy material since small amounts of tissue are required.

Publications

Gomes M, Santella RM: Immunologic Methods for the Detection of Benzo(a)pyrene Metabolites in Urine. Chemical Research in Toxicology 3:307-310, 1990

Santella RM, Li Y, Zhang YU, Young TL, Stefanidis M, Lu XQ, Lee BM, Gomes M, Perera FP: Immunologic Methods for the Detection of Polycyclic Aromatic Hydrocarbons-DNA and Protein Adducts. In: Genetic Toxicology of Complex Mixtures, (ed M Waters) Plenum Publishing Corporation, in press, 1990

Zhang YJ, Li Y, DeLeo VA, Santella RM: Detection of DNA Adducts in Skin Biopsies of Coal Tar Treated Psoriasis Patients: Immunofluorescence and ^{32}P Postlabeling. Skin Pharmacology, in press, 1990

Mechanisms of Cytoskeletal Injury by Ni Compounds

Ken C. Lin
Boston University
School of Medicine
Department of Pathology
80 East Concord Street
Boston, Massachusetts 02118-2394

Program Area: *Dermatologic Conditions*
Grant Number: *5 R03 OH02655-02*
Start & End Dates: *06/01/89 – 05/31/91*
Funding Level: *$25,590 ($51,845 Cum)*

Importance to Occupational Safety and Health

Nickel (Ni) is a well-documented respiratory tract carcinogen among nickel refinery workers involved in high-exposure operations such as

grinding, calcining, sintering, and leaching. Evidence from the British epidemiologic studies showed that nickel refinery workers had a five-fold increase in lung cancer and as high as 150-times increase in nasal sinus cancer compared to the control. Many cases of severe acute and even fatal toxicity have also been reported following nickel carbonyl exposure. Furthermore, Ni is also notorious for inducing nickel contact dermatitis, one of the most common forms of allergic contact dermatitis. Indeed, recent data indicate that Ni accounts for 8% of the cases of occupational dermatitis, which is already the most prevalent occupational disease, and that Ni is the major allergen for women with whom large increases in the number of cases have been reported. Moreover, Ni and its compounds are widely used in a variety of industries including alloys (e.g. stainless steel), electroplating, Ni-Cd battery, electronics, textile production, chemical manufacture, petroleum refining, edible oil hardening, food additive, etc. Thus, the ubiquity of occupational exposure to Ni in workplaces highlights the importance to gain a clear understanding of mechanisms of Ni toxicity and carcinogenesis. With the advent of new insights into cytoskeletal dynamics, more evidence is revealed concerning the association of cytoskeletal changes with a wide variety of human pathological conditions. Moreover, Ni, like several other heavy metals [e.g. Cd(II), Pb(II), As(III)], has been shown to cause severe damage to microtubules, one of the major components of the cytoskeleton. This proposal intends to investigate the possible role of the cytoskeleton in mediating cellular injuries by Ni compounds.

Objectives

The goal of this project is to elucidate the mechanisms by which Ni-induced cytoskeletal perturbation occurs in cultured 3T3 cells exposed to Ni, and its relationship to cell injury and possibly carcinogenesis. Effect of Ni on the *in vitro* polymerization of purified microtubule proteins containing tubulin and microtubule associated proteins (MAPs) will be investigated. Since MAPs play an important role in the polymerization and stabilization of microtubules, the phosphorylation state and distribution of MAPs and their isoelectric variants will also be examined. With growing evidence of physical linkage between organelles and the cytoskeleton, Ni-induced microtubule change may also result in a redistribution and possible damage in the normal function of cytoplasmic organelles such as mitochondria, the Golgi apparatus, ER, etc. Alteration in the function of vital organelles such as the mitochondria may lead to an imbalance of nucleotide pools which may contribute to the observed chromosomal damage observed in cells exposed to Ni. These issues will be investigated.

Methodology

For the experiments involving *in vitro* microtubule assembly, bovine brain microtubule protein is purified according to the temperature-dependent disassembly/assembly method. Assembly of microtubules *in vitro* is done at 27°C and monitored spectrophotometrically by measuring the increase in turbidity. Continuous recording of turbidity of each experiment is provided by a Perkin Elmer R100A chart recorder connected to the spectrophotometer.

For analysis of MAPs *in situ*, metabolic labeling of 3T3 cells and 2-dimensional gel electrophoresis are employed. Cells are metabolically labelled with [^{35}S]-methionine or/and ^{32}Pi, then selectively extracted with detergent and $CaCl_2$. The extracted fractions are analyzed via 2-D gel electrophoresis as described by O'Farrell.

To investigate the possible redistribution of organelles induced by Ni, vital stains are used. $DiOC_6$, a cyanine dye, selectively stains mitochondria at low doses and ER at higher doses. The Golgi apparatus can be visualized by C_6-NBD-ceramide label. Stained 3T3 cells will be examined under a fluorescence microscope.

For nucleotide pool analysis, the total cellular acid-soluble nucleotides of 3T3 cells are extracted with ice-cold TCA and analyzed by a Waters high-pressure liquid chromatography (HPLC) on Whatman's Partisil-10 SAX ion exchange columns.

Significant Findings

To understand the mechanism of the Ni^{2+}-induced MT change, we investigated the effect of Ni^{2+} (0.01 to 3.0 mM) on *in vitro* tubulin polymerization. Ni^{2+} at lower concentrations (0.01 to 1.0 mM) had little or no significant effect on the kinetics of MT polymerization. In contrast, in the presence of 1.5 to 2.0 mM Ni^{2+}, a significant promoting effect on both the rate and the final extent of polymerization was observed. However, at Ni^{2+} concentrations higher than 2.0 mM, such stimulatory effect on the rate and the final extent of tubulin polymerization declined. Furthermore, the promoting effects of Ni^{2+} on MT polymerization were accompanied by a significant decrease in the lag period. Electron microscopic examination of samples of the polymerization product showed that MT, polymerized in the presence of 2.0 mM Ni^{2+}, appeared more numerous and shorter (1.10±1.02

μm) than those of control (3.81±2.29 μm). This was probably a direct result of an increase in the number of initiation centers in the presence of Ni^{2+} as a consequence of the decreased critical concentration (7%) necessary for polymerization to occur. Our results suggest that Ni^{2+} may exert its toxic effect on MT in cultured cells by altering the normal kinetics of MT polymerization.

Publications

Lin KC, Andry C, Chou IN: Ni(II) Effect(s) on Microtubule Polymerization. The Toxicologist, 10/111, 1990 (Abstract #441)

Lin KC, Chou IN: Studies on the Mechanisms of Ni^{2+}-Induced Cell Injury: I. Effect of Ni^{2+} on Microtubules. Toxicology and Applied Pharmacology, in press, 1990

Stress in One Occupational Group: Teachers

Irvin Schonfeld, Ph.D.
City College of CUNY
Department of Social
and Psychological Foundations
Convent Avenue at 138th Street
New York, New York 10031

Program Area: *Psychological Disorders*
Grant Number: *5 R01 OH02571-03*
Start & End Dates: *06/01/88 – 05/31/91*
Funding Level: *$95,960 ($252,991 Cum)*

Importance to Occupational Safety and Health

The study examines the effects school conditions exert on teachers' health (e.g., depressive and psychosomatic symptoms), health behaviors (e.g., alcohol consumption and tranquilizer use), and morale (e.g., motivation to continue in the profession and job satisfaction). Despite importance of teachers to our nation's future, teachers' working conditions, particularly in urban public schools, are often unsatisfactory. These conditions include, but are not limited to, student violence and disrespect. The working conditions believed to adversely affect teachers' health and morale are preventable and should inform future efforts directed at job redesign.

Objectives

1. To compare the pre- and post-employment mental health (e.g., depressive symptoms, self-esteem), psychophysiologic symptoms, and health behaviors (e.g., smoking) of recent college graduates who enter the teaching profession with that of similar graduates who do not enter the teaching profession.
2. To identify the types of episodic job-related events and ongoing working conditions that affect the health and morale (job satisfaction, motivation to remain in teaching, and exits from the profession) of new teachers. Alternative measures of job stressfulness (e.g., school-level teacher-assault rates), derived from public records, will also be examined in relation to teacher health.
3. To identify the types of resources, including personal dispositions (e.g., locus of control), social support from colleagues and supervisors, and coping strategies, that may affect health outcomes in teachers. The question of whether the resources directly affect health outcomes or mitigate the effects of the job-related stressors will be investigated.

Methodology

Graduating students from the classes of 1988, 1989, and 1990 are recruited from among senior-year education and psychology courses and followed into their first jobs. With the support of grants from the City University of New York, members of the 1987 cohort are also followed. The colleges from which the seniors graduate staff many positions in metropolitan New York schools. Participants are followed longitudinally by questionnaire for up to three years, with measures obtained on them in the summer before entry into the workforce (Time 0, pre-employment), and then on two more occasions during the academic calendar (Times 1 and 2, generally post-employment). Some teachers are also followed two to three years.

Information on symptoms (psychosomatic and depressive), health behaviors (smoking, coffee drinking, alcohol consumption, tranquilizer use and obesity), non-occupational stressors (e.g., death of a loved one), and social and psychological resources (e.g., social support from colleagues and noncolleagues and locus of control) is obtained. A strength of the study is its prospective design that includes the ascertainment of pre-employment measures of the principal outcomes.

Two concomitant longitudinal studies supported by the University examine the effects of working conditions on blood pressure and affective illness in female teachers. Both studies take advantage of the present longitudinal study. In the blood pressure study, the pressures of 50 women, teachers and nonteachers, are obtained during their final semester (May 1990, the preemployment period) in college and twice more later in the year (November 1990 and April 1991) when many have entered the workforce. In the affective illness study, only women who are scheduled to graduate in June (or August) 1990 and who have sufficiently low levels of affective symptoms on a pre-employment screen qualify for the study. The purpose of the latter criterion is to exclude women with a preexisting affective disorder. In the fall of 1990 and the spring of 1991, every woman with a high level of symptoms is administered a structured psychiatric interview by a blind diagnostician. In addition, a randomly selected woman who is low in symptoms but matched to the highly symptomatic woman for date of screening is also interviewed by

the blind diagnostician. The women in the affective-illness study are teachers and nonteachers. In both the blood pressure and the affective illness studies, the outcomes will be examined in relation to working conditions, which were ascertained in the study supported by NIOSH/CDC. Both the blood pressure and the affective-illness studies are in the field as of this writing.

Significant Findings

Two sets of findings are presented. The first set of findings is limited to women making the transition into teaching and involves the 1987, 1988, and 1989 cohorts. These women typically graduated from college in June and became teachers in September. Multiple linear regression (MLR) analyses examined the effects of the school environment on a number of outcomes, controlling for other factors. The outcomes were measured in the fall of the teachers' first academic year. The other factors included non-occupational stressors and, most importantly, pre-employment measures of those outcomes. The MLR analyses revealed that the frequency of adverse school conditions (e.g., students engaged in fighting), which were measured by neutrally worded self-reports (see Kasl, 1987), was related to increased depressive and psychosomatic symptoms, lower self-esteem, poorer perceived health, diminished job satisfaction (controlling for pre-employment expected satisfaction) and motivation to continue in the profession, and increased tranquilizer use. Analyses conducted by Schonfeld and Ruan (in press) indicated that the scales used to measure the teachers' work environments minimized bias. Not surprisingly, additional analyses failed to find effects of the school environment on smoking, caffeinated coffee drinking, alcohol consumption, and obesity. These behaviors either have relatively low base rates in females (e.g., alcohol consumption) or require more time to yield to change (e.g., obesity).

The second set of analyses refer to structural equation models that examine the development of depressive symptoms into spring semester of the teachers' first year on the job. The analyses indicate that the principal impact of job conditions on depressive symptoms is relatively immediate, occurring as early as the fall, and that the symptoms tend to endure into the spring. In addition, noxious school environments continue to exert effects in the spring.

Publications

Schonfeld IS: Burnout in Teachers: Is It Burnout or Is It Depression? Human Stress: Current and Selected Research, 5, in press, 1990

Schonfeld IS: Dimensions of Functional Social Support and Psychological Symptoms. Psychological Medicine, in press, 1990

Schonfeld IS, Ruan D: Occupational Stress and Pre-employment Measures: The Case of Teachers. Journal of Social Behavior and Personality, in press, 1990

Schonfeld IS: Distress in a Sample of Teachers. Journal of Psychology 123:321-338, 1990

Schonfeld IS: Coping with Job-Related Stress: The Case of Teachers. Journal of Occupational Psychology 63:141-149, 1990

Schonfeld IS, Shaffer D, Barmack JE: Neurological Soft Signs and School Achievement: The Mediating Effects of Sustained Attention. Journal of Abnormal Child Psychology, in press, 1989

Schonfeld IS: Psychology and City College (Co.). American Psychologist, in press, 1989

Schonfeld IS, Rasmussen E, Sims C: Enhancing Undergraduate Achievement in Educational Psychology with Instructional Objectives. Education, in press, 1989

Schonfeld IS, Shaffer D, O'Connor P, Portnoy S: Conduct Disorder and Cognitive Functioning. Testing Three Causal Hypotheses. Child Development 19:993-1007, 1989

Trautman C, Erickson D, Shaffer D, Correra A, Schonfeld IS: Prediction of Intellectual Deficits in Children with Acute Lymphocytic Leukemia. Journal of Developmental and Behavioral Pediatrics 19:122–128, 1989

Fundamental Investigation of Exhaust Hoods

Nurtan A. Esmen, Ph.D.
University of Pittsburgh
Graduate School of Public Health
130 DeSoto Street
Pittsburgh, Pennsylvania 15261

Program Area: *Control Techniques*
Grant Number: *2 R01 OH02132-04*
Start & End Dates: *05/01/85 - 12/31/89*
Funding Level: *$68,689 ($339,963 Cum)*

Importance to Occupational Safety and Health

This research is expected to produce a general optimization scheme to improve the efficiency of local exhaust hoods, which will reduce worker exposure as well as the cost of operating the exhaust system.

Objectives

The long-term objective of this project is the optimization of exhaust hoods used in industrial ventilation, maximizing the capture ability and minimizing the air flow through the hood.

Methodology

In order to carry out an optimization process, it is necessary to obtain tractable mathematical expressions of air flow generated by exhaust hoods under a wide range of circumstances which describe the operating parameters of the exhaust hoods as they may be used in an industrial operation. This portion of the study was carried out by obtaining the needed expressions utilizing potential flow theory and representative sink matching. The equations obtained were verified experimentally by the standard techniques of hot wire anemometry. The capture efficiency of hoods are being investigated using neutrally generated acetone vapor as the contaminant with air turbulence super-imposed upon the velocity field by means of a wake generated by a grid.

Significant Findings

In the research carried out to date, we were able to construct mathematical expressions to predict air flow induced by free-standing flanged exhaust hoods and experimentally verify these equations. The extension of these mathematical expressions to conditions where planes are adjacent to the hood at an arbitrary angle, and the experimental verification of these expressions, enabled us to extend the theoretical work to design conditions encountered often in the industry. The second, probably more significant accomplishment, was to develop a relatively simple optimization scheme for free standing exhaust hoods.

Relative to the original aims of the project, the accomplishments to date gave an optimization process which can be applied widely. The current research should provide the required design safety factor to extend the optimization procedures to a very wide variety of industrial situations.

Publications

Esmen NA, Weyel DA: Air Flow Generated by Flanged Suction Hoods with Adjacent Planes. Ventilation '88. (ed. JH Vincent), Pergamon Press, London, in press, 1988

Esmen NA, Weyel DA: Optimization of Freely Suspended Exterior Hoods in Industrial Ventilation. Proceedings VIIth International Pneumoconioses Conference, in press, 1988

Esmen NA, Weyel A, Pirris A, Ilori AG: Aerodynamics of Arbitrarily Shaped Orifice Exterior Hoods. Ann Occup Hyg, in press, 1988

Durr DE, Esmen NA, Stanley C, Weyel DA: Pressure Drop in Flexible Ducts. Applied Ind Hyg 2:99-102, 1987

Durr DE, Esmen NA, Stanley C, Weyel DA: Pressure Drop in Elbows. Applied Ind Hyg 2:57-60, 1987

Esmen NA: Numerical Expressions for Ventilation Parameters. Ventilation '85. (ed. HD Goodfellow), 735-743, 1986

Esmen NA, Weyel DA: Aerodynamics of Multiple Orifice Hoods. Ventilation '85. (ed. HE Goodfellow), 735-743, 1986

Design a Systematic Engineering Control for Robotic System Safety

Bernard C. Jiang, Ph.D.
Auburn University
Industrial Engineering Department
207 Dunstan Hall
Auburn University, Alabama 36849-5346

Program Area: *Control Techniques*
Grant Number: *5 R01 OH02230-02*
Start & End Dates: *01/01/88 - 12/31/89*
Funding Level: *$18,859 ($53,490 Cum)*

Importance to Occupational Safety and Health

As more and more robots are used in the workplace, the proper design of the robotic system becomes more important to prevent injuries. A review from this study showed that most robot-related accidents are preventable if the robotic system is properly designed and controlled. The study results provide a review of robot-related accidents, a review of guarding techniques for robots, a set of detailed guidelines for the planning, installation, and operation stages of robot use, and the principles and implementation of the design and control of a robotic cell. The study results can be applied to existing robots as an evaluation tool and to future robotic systems as a design guideline, thereby making the developed control system particularly useful for minimizing potential accidents that might be caused by robot use.

Objectives

The objectives of this study are to develop a systematic procedure and guidelines for designing a robotic system, to construct a physical robotic system safety model according to the developed procedure, and to develop an intelligent software control system for monitoring the safety of the robotic system.

Methodology

The study consisted of three phases. In Phase I, a systematic procedure and guidelines were developed for designing a robotic safety system. In phase II, a physical robotic safety model cell was constructed. In Phase III, an intelligent software control system was developed for monitoring the robotic system.

Significant Findings

It has been concluded from the results of this research that a robot cannot be considered as an individual unit in a manufacturing system, nor can any component (human operator, robot, robot controller, environment, or operational process) in a robotic system be separated and still effectively prevent robot-related accidents.

Specifically, the following information resulting from this research is useful to the robotic system designer and user:

1. A review of the previous robot-related accidents data: From the analysis of the recorded 32 robot-related accidents, most of the accidents would have been prevented if appropriate safety design considerations were in effect.
2. Systematic engineering control guidelines for designing a robotic cell were developed: These guidelines are presented in the same format as a procedure analysis. The guidelines include planning, installation, and operation stages of robot use. The dangers, causes, effects and corrective measures are provided for each task in a certain stage of robot use. These easy-to-follow guidelines can be adjusted for a specific robotic application.
3. A review of the available machine guarding techniques for robot guarding: The review results show that most of the guarding techniques are still applicable to industrial robots with modifications to accommodate differences. This review is important not only from the standpoint of robotic applications, but also as a response to an unanswered question: "Should robots be treated as traditional machines?"
4. Design for robotic cell safety: A robot usually works with other machines in a manufacturing system. When considering safety, attention should be given not only to the individual machines and robots, but also to their interactions to meet processing needs. The six severity level design (SSLD) concept was presented for safely designing a manufacturing cell. This design philosophy integrates guarding techniques with control actions, considers both production needs and safety concerns, and interfaces machine functions with process requirements. This philosophy has been implemented in an unmanned manufacturing cell that makes a family of parts. The hardware and software, as well as their interactions with the manufacturing process and control actions, are described. The designed system has the advantage of providing maximum protection to

the operators while causing minimum interruption in production.

Publications

Jiang BC, Cheng OSH: Six-Severity-Level Design for Robotic Cell Safety. In: Human-Robot Interaction, (eds. M Rahimi, W Karwowski), Taylor and Francis, in press, 1990

Jiang BC, Cheng OSH: Designing A Safe Robotic Cell. Robots 14 Conference Proceedings, Detroit, Michigan, pp 5-27 to 5-41, November 11-15, 1990

Jiang BC, Cheng OSH: Designing A Safe Robotic Cell. Robotics Today 3(4)1-4, 1990

Jiang BC, Cheng OSH: Design for Robotic Cell Safety. Journal of Manufacturing Systems 9:169-175, 1990

Jiang BC, Cheng OSH: A Procedure Analysis for Robot System Safety. International Journal of Industrial Ergonomics 6:95-117, 1990

Jiang BC, Liou AYH, Suresh N, Cheng OSH: An Evaluation of Machine Guarding Techniques for Robot Guarding. Robotics 7(4), 1990

Liu YS, Jiang BC: From Machine Guarding to Robot Guarding - A Review. In Advances in Industrial Ergonomics and Safety I, (ed. A Mital), Taylor & Francis, London, England, pp 623-630, 1989

Jiang BC, Gainer CA: A Cause-and-Effect Analysis of Robot Accidents. Journal of Occupational Accidents Vol 8:27-45, 1987

Ventilation for Work in Confined Spaces

Richard P. Garrison, Ph.D.
University of Michigan
School of Public Health
Ann Arbor, Michigan 48109-2029

Program Area: *Control Techniques*
Grant Number: *5 R01 OH02329-03*
Start & End Dates: *01/01/87 - 12/31/90*
Funding Level: *$98,997 ($285,336 Cum)*

Importance to Occupational Safety and Health

Accidents during work in confined spaces (CS) have resulted in serious injuries and deaths - roughly 200-300 fatalities each year in the United States. The majority of CS accidents are caused by air contaminants which are either toxic, flammable, or cause oxygen deficiency. There may also be instances of overexposure to airborne chemicals, but very little is known on this issue.

Ventilation is recognized as a primary means of engineering control – a means by which hazardous atmospheres are changed and rendered less hazardous (which administrative controls do not accomplish). Relatively little is known pertaining specifically to CS ventilation design. This lack of knowledge has diminished awareness and emphasis by industry for implementing ventilation for work in confined spaces. It also weakens the ability of agencies such as NIOSH to recommend effective guidelines, and OSHA to enforce safe procedures.

This study is directed toward the need for more knowledge on how to ventilate confined spaces. It will hopefully lead to greater awareness and action to use ventilation and help prevent needless accidents, injuries, and deaths.

Objectives

The overall objective of this project is to advance the state of knowledge of CS ventilation design. More specifically, this study strives to:

1. Observe and evaluate ventilation characteristics of CS laboratory models and describe guidelines for effective ventilation design.
2. Establish an empirical (regression) database that represents the experimental characteristics which can be useful in the development and evaluation of computer models to aid in CS ventilation design.
3. Develop and evaluate computer modeling to approximate contaminant dispersion and ventilation effectiveness in CS models.

Methodology

Laboratory testing investigates ventilation characteristics for different CS model shapes and sizes, ventilation design parameters, and contaminant characteristics. CS model variations have included cubical and noncubical shapes with a single top opening. The noncubical shapes involved expansions, vertically and/or horizontally, from a basic cubical model. Cubical shapes were used to evaluate characteristics of geometric similarity between two models of significantly different size.

Ventilation design parameters included ventilation mode (exhaust vs. supply), volume flowrate (ACH, "air changes" per hour), and inlet/outlet elevation (%H, percentage of CS model height). Studies of contaminant characteristics focused upon recovery from oxygen deficiency caused by gases of different specific gravity (SG): nitrogen, carbon dioxide, chlorodiflouromethane, and sulfur hexafluoride (SG = 0.98, 1.5, 3.0, 5.0, respectively). Characteristics of "trace" (lower concentration) contaminants were tested using isobutylene.

Air samples were drawn from four locations inside the CS models. Analyses involved two primary methods: (1) oxygen deficiency–using a four-channel monitor with electrochemical oxygen sensors, and (2) "trace" characteristics–using a portable gas chromatograph with a photoionization detector. Ventilation flowrates were measured with a calibrated orifice plate.

Experimental data were regressed against an exponential model. The rates of recovery from contaminated to ambient concentrations were represented by recovery time constants, forming an empirical database for CS ventilation design.

Computer models for contaminant dispersion and ventilation effectiveness focused upon a multicellular method which predicted oxygen recovery characteristics reasonably well. Initial estimates of airflow patterns were based upon experimental observation and approximation. Subsequent efforts were made to utilize FEM (Finite Element Method) and BIEM (Boundary Integral Element Method) to model CS airflow characteristics.

Significant Findings

Significant findings from this study include the following:

1. Mechanical ventilation was effective in eliminating oxygen deficiency in a variety of CS model, ventilation, and contaminant situations.
2. Supply ventilation was more effective than exhaust ventilation. CS locations aligned with the supply outlet experienced very rapid oxygen recovery.
3. Inlet/outlet elevation had significant effects upon ventilation effectiveness, with low I/O elevation generally preferable to high.
4. Ventilation time decreased with increasing flowrate, but not always in a simple linear manner, and sometimes with a limit above which increasing flowrate had relatively little effect.
5. Changes in CS model shape had significant, variable, and somewhat inconsistent effects upon ventilation time.
6. Geometric similarity and equal nondimensional flowrate (ACH) were necessary and sufficient for cubical CS models of different size to demonstrate very similar ventilation characteristics.
7. Ventilation effectiveness (oxygen recovery) characteristics varied significantly with contaminant stratification, and oxygen recovery was slower for increasing contaminant SG.
8. A multicellular contaminant dispersion computer model was able to predict ventilation effectiveness reasonably well for situations involving purging, continuous, and variable rates of contaminant release.
9. The BIEM provided reasonably good predictions of velocity characteristics for the multicellular model in the case of exhaust ventilation; predictions were not as good for supply ventilation.
10. Dilution ventilation characteristics for "trace" contaminants were similar to those for oxygen deficiency.

Publications

Garrison RP, Erig M: Ventilation to Eliminate Oxygen Deficiency in a Confined Space - Part Three: Heavier-than-Air Characteristics. Applied Occ & Env Hyg, in press, 1990

Park C, Garrison RP: Multicellular Model for Contaminant Dispersion and Ventilation Effectiveness with Application for Oxygen Deficiency in a Confined Space. Am Ind Hyg Assoc J 50:70-78, 1990

Garrison RP, Nabar R, Erig M: Ventilation to Eliminate Oxygen Deficiency in a Confined Space - Part One: A Cubical Model. Applied Ind Hyg 4:1-11, 1989

Garrison RP, Erig M: Ventilation to Eliminate Oxygen Deficiency in a Confined Space – Part Two: Non-Cubical Models. Applied Ind Hyg 4:260-268, 1989

Artificial Intelligence in Process Plant Safety

Venkat Venkatasubramanian, Ph.D.
Purdue University
School of Chemical Engineering
Laboratory for Intelligent Process Systems
West Lafayette, Indiana 47907

Program Area: *Control Techniques*
Grant Number: *5 R01 OH02352-02*
Start & End Dates: *06/01/88 - 08/31/90*
Funding Level: *$59,219 ($141,129 Cum)*

Importance to Occupational Safety and Health

Modern chemical plants are extremely complex and, as witnessed by recent plant accidents, are more vulnerable to equipment failures. Because of this complexity, modern plants are also more difficult to diagnose, thus raising serious occupational safety-related problems. We are also dealing more with toxic substances, and with the advent of biotechnology and genetic engineering industries, the results of an industrial accident can be quite devastating. Occupational safety and health hazards pose a serious threat to an estimated 80 million workers in the United States. Industrial statistics show that even though major catastrophies and disasters of chemical plants are infrequent, minor accidents are very common. They occur on a day-to-day basis, resulting in many occupational injuries and illnesses, and costing the society billions of dollars every year. During 1983, the Bureau of Labor Statistics reported over 3,000 job-related deaths and estimated 4.9 million job-related injuries and illnesses. It is also estimated that the annual cost to society of work-related injuries, illnesses, and deaths has nearly tripled from $11.5 billion in 1972 to $33.0 billion in 1984.

The proposed project is aimed at the prevention and control of such frequent, day-to-day, accidental events in the industry. The proposed research would lead to a better understanding of the complexities that are involved in the design of computer systems that can effectively monitor, diagnose, and control chemical plants. In this project, we propose a model-based reasoning methodology that has considerable potential in the development of such intelligent systems.

Objectives

The major goal of this proposal is to research and demonstrate new approaches based on Artificial Intelligence (AI) towards the design of chemical process hazard detection, prevention, and control systems. Such systems are extremely important for improving the occupational safety of chemical plants owing to the complexity of modern process plants. The proposed project is aimed at the prevention and control of chemical plant accidents through the development of model-based diagnostic reasoning methodologies using artificial intelligence techniques.

Methodology

Past approaches in fault diagnostic systems did not properly include the human expert's reasoning strategies and experience, and hence were not adequate in efficient and correct trouble-shooting. This is largely due to the fact that the past attempts did not incorporate AI techniques, an essential ingredient. Knowledge-based systems, utilizing the proposed methodology, diagnose by using a combination of first-principles knowledge and compiled experiential knowledge rather than compiled knowledge alone, as many expert systems now do. The methodology centers around the idea of utilizing a library of causal and fault models of the process units during the diagnostic reasoning process. As these models are generic and process-independent, they are applicable to a wide variety of process configurations. This deep-level knowledge of the process is integrated with compiled process specific heuristics in an object-oriented two-tier architecture.

Significant Findings

We have demonstrated the feasibility of this novel approach in the form of a prototypical expert system, called MODEX2 (Model Oriented Diagnostic EXpert2), that has been developed for prototypical chemical plants. An object-oriented architecture has been developed for facilitating knowledge representation and reasoning. We have also developed a framework for the integration of deep-level and compiled knowledge for process diagnosis. We have also demonstrated the automatic acquisition of diagnostic knowledge through a mechanism called causality-based failure-driven learning. We have also developed a framework for systematically generating the causal models from first-principles knowledge of process relationships. Furthermore, we have developed a technique for the automatic generation of process

trend descriptions from sensor data. This trend description is used to perform diagnosis under transient conditions of the process.

Publications

Rich SH, Venkatasubramanian V, M Nasrallah, Matteo C: Development of a Diagnostic Expert System for a Whipped Toppings Process. J Loss Prev Process Ind, July, pp 145-154, 1989

Rich SH, Venkatasubramanian V: Causality-Based Failure-Driven Learning in Diagnostic Expert Systems. AIChE Journal 35, 6:943-950, 1989

Venkatasubramanian V, Rich SH: An Object-Oriented Two-tier Architecture for Integrating Compiled and Deep-Level Knowledge for Process Diagnosis. Computers and Chemical Engineering, 12,9/10:903-921, 1988

Fundamental Factors that Affect Dust Generation

David Leith, Sc.D.
University of North Carolina
Department of Environmental Sciences and Engineering
Rosenau Hall, CB #7400
Chapel Hill, North Carolina 27599

Program Area: *Control Techniques*
Grant Number: *5 R01 OH02437-02*
Start & End Dates: *12/01/88 - 11/30/90*
Funding Level: *$79,702 ($157,372 Cum)*

Importance to Occupational Safety and Health

Powders and granulated solids are used throughout industry. Wherever these materials are handled, they generate dust that can affect worker health, cause a safety problem, and cause a nuisance.

Factors that affect dust generation are important but poorly understood. Information about these factors is necessary: (1) to develop product specifications for the dustiness of industrial materials, (2) to assess the inherent dustiness of processes and materials, important for the pre-manufacture notification requirements of TOSCA, and (3) to evaluate changes to materials or processes that can control dust problems.

Objectives

This project addresses these needs by seeking to achieve three objectives:

1. Develop a test that measures dustiness. We developed a method to evaluate the generation rate and size distribution (dustiness) of dusts generated by handling granular materials.
2. Use the test to understand factors that affect dustiness. We investigated quantitatively the dependence of dust generation rate and size distribution on factors that affect dustiness.
3. Evaluate measures by which dustiness can be controlled. Using results from the above, we evaluated means by which industrial dust problems can be controlled.

This research will help characterize sources of industrial dusts and will help develop understanding that allows dust generation to be minimized at those sources. As a result of this research, health and safety problems related to dust exposure will be assessed and controlled more reliably.

Methodology

We have developed a test that measures simultaneously the generation rate and size distribution of dust produced under conditions that simulate handling of granular materials in industry. In this test, material drops at a constant rate from a known height into a hopper with a receiving pile that has constant height. The generated dust is carried to an elutriation column that removes particles larger than 25 μm in aerodynamic diameter. At the outlet of this column is a high-volume cascade impactor that sorts these particles by aerodynamic size. Air entrained with the column of falling material is measured independently with a bleed system. We have conducted experiments to measure the reproducibility of this test procedure, as well as the generation rate and size distribution of an aerosol produced by dropping materials that include sand, limestone, flour, and cement with various drop heights, mass flow rates, moisture contents, and size distributions.

Significant Findings

Results of these experiments showed that this test method gives reproducible results, and that the variables tested here affect generation rate and size distribution with the following order of importance: (1) moisture content, (2) drop height, (3) size distribution, and (4) mass flow rate. Different

materials respond to the same test in different ways. These findings can be explained through a balance between the binding forces that keep granular materials together and the separation forces that act when the material is handled. Results from this work are correlated mathematically through an equation that predicts dust generation for particles of given size.

Computer Simulation of Push-Pull Systems

Michael R. Flynn, Sc.D.
University of North Carolina
School of Public Health
Environmental Sciences and Engineering
CB 7400 Rosenau, Room 118
Chapel Hill, North Carolina 27599-7400

Program Area: *Control Techniques*
Grant Number: *1 R01 OH02710-01*
Start & End Dates: *09/01/90 - 08/31/92*
Funding Level: *$81,777 ($81,777 Cum)*

Importance to Occupational Safety and Health

This research seeks to improve the design of local exhaust ventilation systems that are augmented by the use of push jets. These systems are used to control worker exposure to toxic airborne contaminants from numerous industrial processes, e.g., open surface tank operations.

Objectives

The specific objectives are to (1) develop a computer code to solve the three-dimensional continuity and Navier-Stokes equations governing the flow of a hood, jet, and crossdraft, and (2) validate the computer predictions of velocity, capture efficiency, and contaminant distribution with wind tunnel tracer studies.

Methodology

Galerkin and/or Petrov-Galerkin finite element techniques will be used initially to approximate the three-dimensional velocity and concentration fields. Validations will include hot-film anemometry, flow visualization, and concentration measurements using sulfur hexafluoride as a tracer. Infrared spectrophotometry will be the detection method.

Significant Findings

None to date.

Field Study of Local Exhaust Ventilation Performance

Lorraine M. Conroy, Sc.D.
University of Illinois at Chicago
School of Public Health
EOHS (M/C 922)
P.O. Box 6998
Chicago, Illinois 60680

Program Area: *Control Techniques*
Grant Number: *5 K01 OH00078-02*
Start & End Dates: *09/28/89 - 09/27/92*
Funding Level: *$18,886 ($70,863 Cum)*

Importance to Occupational Safety and Health

A model which can be used to predict capture efficiency for flanged slot hoods exhausting area sources in the presence of a uniform crossdraft has been developed and validated under controlled laboratory conditions. This project will field validate the capture efficiency model for vapor degreasers exhausted with exterior type hoods, quantify industrial crossdrafts, and correlate process and worker activities with capture efficiency and crossdraft measurements.

The research will lead to (1) an improved method for predicting hood capture efficiency and improved hood design methods; and (2) a better and more systematic evaluation of industrial crossdrafts, including the turbulence characteristics of these crossdrafts. Improved hood design methods, combined with a better understanding of the characteristics of industrial crossdrafts, will result in improved air quality in plants using vapor degreasers, lower probability of health hazards and safety hazards associated with air concentrations of halogenated solvents, and possibly lower operating costs if the solvent is recovered from the local exhaust system.

Objectives

The broad long-term objective of this research is to answer the question: Can exterior hood design be improved to adequately control emissions from open surface tanks? The specific

aims of the research are to answer the following questions: (1) Can laboratory validated capture efficiency models be used to predict capture efficiency of local exhaust hoods in industrial settings? (2) Can industrial crossdrafts be quantified and characterized? (3) Can activity parameters be correlated with measured crossdrafts and capture efficiencies?

Methodology

The project involves conducting eighteen field studies, six in the first year and twelve in the second year, at a rate of one per month. Three sets of measurements will be done during each study to answer the questions asked in the specific aims.

During idling conditions, tracer gas will be released through a series of tubes with holes drilled in them, configured to fit over the surface of the vapor degreaser. Sulfur hexafluoride (SF6) will be released at a measured rate and the concentration of SF6 will be measured in the duct downstream of the hood. The air flow will be measured, along with the hood and tank dimensions. These measurements will allow for calculation of capture efficiency. Simultaneously with the SF6 measurements and during operational periods, solvent concentration will be measured in the duct and at several distances from the degreaser. This will allow for calculation of emission rates from Fick's Law and the concentration gradient. The duct concentration and emission rate will also allow for calculation of capture efficiency.

The simultaneous measurements will give independent validation of the emission factor approach as a method of measuring local exhaust hood capture efficiency. The SF6 measurements will be limited to idling conditions because the SF6 release apparatus will interfere with operation of the degreaser. The emission factor approach will be used to measure hood capture efficiency during production times.

Crossdraft velocity (magnitude and direction) will be measured simultaneously with measurement of capture efficiency using a two-dimensional hot-wire anemometer.

Capture efficiencies measured each hour will be compared with model predictions. The magnitude of the crossdrafts will be tabulated for use in the design and operation of local exhaust systems as well as design of future experimental work. The turbulence characteristics of the crossdrafts will be measured. These characteristics will be analyzed to determine how close (or different) they are from those used in the laboratory development of the capture efficiency model. The model may need to be adjusted for any significant differences.

Activities involving the degreaser (loading, unloading of parts; opening, closing of cover; size, shape of parts; etc.) and activities in the vicinity of the degreaser (workers walking, standing, sitting near the degreaser; use and location of cooling fans; location of general ventilation supply and exhaust openings; etc.) will be recorded during each hour that sampling is conducted. Recorded activities will be correlated with recorded crossdrafts to determine how specific activities are related to measured crossdraft characteristics.

Significant Findings

Seven field studies have been conducted to date. Preliminary data analysis indicates that the emission factor approach gives a valid measurement of capture efficiency and that the capture efficiency model can be used to predict local exhaust hood performance under operating conditions.

Glove Permeation by Semiconductor Processing Mixtures

Edward T. Zellers, Ph.D.
University of Michigan
School of Public Health
Department of Environmental and Industrial Health
109 South Observatory
Ann Arbor, Michigan 48109-2029

Program Area: *Control Techniques*
Grant Number: *1 R03 OH02667-01*
Start & End Dates: *07/01/89 – 06/30/90*
Funding Level: *$23,834 ($23,834 Cum)*

Importance to Occupational Safety and Health

The permeation of solvents through gloves and subsequent dermal absorption may represent an important route of exposure to hazardous chemicals used in semiconductor microfabrication facilities. Of particular concern are organic solvent mixtures containing glycol-ether (cellosolve) derivatives, several of which are recognized reproductive hazards that are readily absorbed through the skin. In addition, new formulations are being introduced that contain dermally mobile solvents for which little or no toxicological or glove permeation data are available. Published guidelines contain very limited data on the effect of temperature, repeated

exposure, and solvent mixtures on the permeation resistance of CPC materials. While several models for predicting solvent permeation through CPC are being developed, no generally applicable model has emerged to date. Thus, determining the proper glove to use under a given set of conditions requires empirical testing.

The results of this study should aid in the assessment and control of dermal exposures to hazardous chemicals in the semiconductor industry. Examination of the data in light of various models of permeation should allow determination of the applicability of such models to the problem of mixed-solvent permeation and lead to an improved model for predicting solvent permeation through protective clothing.

Objectives

The primary objective of this study was to characterize the permeation behavior of several glove materials when challenged with organic solvent mixtures used in semiconductor manufacturing processes. The effects of temperature and repeated exposure were also investigated. The broader objectives were to provide information that would be useful in the evaluation of potential risks from dermal exposure to hazardous solvent mixtures and in the proper selection and use of gloves in semiconductor processing facilities. Correlations between the observed results and those predicted by each of several models are being examined to determine whether the permeation of untested mixtures could be predicted. A new model for predicting permeation has also been developed.

Methodology

Five chemically protective glove materials commonly used in microfabrication facilities were tested at 25 and 37°C using standard permeation test methods. Solvents and formulations examined included positive and negative photoresists, a positive photoresist thinner, 2-methoxyethyl acetate (an electron-beam resist solvent), propylene glycol monoethyl ether acetate (a newer positive resist solvent), and N-methyl-2-pyrrolidone (NMP, a high-temperature degreasing solvent). The effects of repeated exposure and thermal decontamination were examined for gloves showing the best initial levels of permeation resistance. Results are being compared to those predicted by permeation models based on immersion weight gain, molecular group contribution methods, and solubility parameters. Predicted results from a new model have been compared to previously reported experimental data for Viton^{R} challenged with 18 organic solvents.

Significant Findings

With the exception of the negative photoresist, butyl rubber provided the highest level of protection against the solvent mixtures tested, with no breakthrough being observed after four hours of continuous exposure at 25°C. Nitrile rubber provided the highest level of protection against the negative photoresist, and reasonably good protection against initial exposure to the other solvent mixtures. Gloves consisting of natural rubber or natural rubber blends provided less protection against the mixtures than either nitrile or butyl rubber. For most of the glove samples, permeation of the glycol-ether derivatives contained in the mixtures was faster than that predicted from the permeation of the pure solvents. With the exception of butyl rubber, increasing the exposure temperature from 25 to 37°C resulted in decreases of 25-75% in breakthrough times and increases of 80-457% in steady-state permeation rates relative to values obtained at 25°C. Repeated exposure of nitrile rubber samples resulted in shorter breakthrough times for all mixture components. With the exception of the negative photoresist, heating previously exposed nitrile rubber samples at 70°C for 20 hr prior to re-testing reduced or eliminated the effects of residual solvents, permitting re-use of the gloves. Initial results of testing natural rubber gloves with NMP (testing is still in progress) indicate dramatic reductions in permeation resistance with increasing temperature, but no evidence of persistent permeation.

The new permeation model employs explicit expressions derived from polymer solution theory that relate the solubility parameters of a given CPC-polymer and solvent to the equilibrium solubility of the solvent in the polymer. Estimated solubility values for 18 solvents in Viton^{R} were combined with estimated diffusion coefficient values to predict breakthrough times under the assumption of Fickian diffusion. Predicted breakthrough times were within a factor of 3 of experimental values for 16 out of 18 solvents. Modifications to account for temperature and the presence of solvent mixtures are being explored.

Publications

Zellers ET: Predicting Solvent Permeation Through Chemical Protective Clothing Using Solubility Parameters: A New Model. American Industrial Hygiene Conference and Exposition, Salt Lake City, Utah, May 18-25, 1991, in press (Abstract)

Capture Efficiency of Local Exhaust Hoods

Lorraine M. Conroy, Sc.D.
The University of Illinois
School of Public Health, EOHS (M/C 922)
P.O. Box 6998
Chicago, Illinois 60680

Program Area: *Control Techniques*
Grant Number: *5 R03 OH02680-02*
Start & End Dates: *08/01/89 - 07/31/91*
Funding Level: *$23,583 ($40,096 Cum)*

Importance to Occupational Safety and Health

While the recent developments in the design of local exhaust hoods are significant, further research is needed before any of these models become practical. The work reported in the literature to this point, including that of the principal investigator, has been conducted in the laboratory under controlled conditions. The variable of ultimate interest to industrial hygienists is not capture efficiency or capture velocity, but breathing zone concentration of contaminant. Future research must attempt to relate hood capture efficiency with breathing zone concentration for a variety of hood, worker, and extraneous air flow conditions. An important component of improved capture efficiency models must be a better understanding of the nature of the turbulence which characterizes exterior hood performance. Such understanding is important because turbulence affects both hood capture efficiency and the subsequent transport of contaminant to the breathing zone of the worker.

The research outlined here proposes to address this last issue. The turbulence parameters of typical crossdrafts or air flow disturbances will be investigated and tabulated. Existing capture efficiency models developed for uniform crossdrafts will be used as the starting point for new model development. This new model will include the effects of turbulence scale and intensity on the spread of contaminant around streamlines.

Objectives

The broad long-term objectives of any research of capture efficiency of local exhaust hoods should be: (1) to develop usable, practical, and validated models to predict hood performance; (2) to relate hood capture efficiency to workers' breathing zone concentration; and (3) to develop methods of ventilation design to maintain workers' breathing zone concentration below a specified level (e.g., Permissible Exposure Level, PEL, or Threshold Limit Value, TLV). The specific aims of this research proposal are: (1) to investigate the turbulence parameters (intensity and scale) of typical crossdrafts or disturbances to air flow; and (2) to incorporate turbulence parameters into existing capture efficiency models.

Methodology

The first step in this research project is to investigate the turbulence parameters scale and intensity) of typical crossdrafts or air flow disturbances. Four different situations are being studied:

1. An obstruction, such as a person, in the flow field.
2. A person walking near a local exhaust hood.
3. A draft through a door due to room pressure differentials.
4. A draft created by a cooling fan.

The velocity ln each of the situations listed will be measured, in a grid pattern in the area in front of the hood, using a hot-film anemometer with high frequency response suitable for turbulence recording. Velocity as a function of time will be recorded on a personal computer with an analog to digital converter. Turbulence intensity is defined as the square root of the sum of the square of velocity fluctuation divided by the mean velocity. Turbulence scale is determined by performing a fast Fourier transform on the velocity data to get a power spectrum. Examination of the power spectrum reveals the scale of turbulence. A series of tables or graphs will be generated from the velocity and turbulence data for the four situations studied.

The second step is to develop a predictive model for capture efficiency which includes the effects of turbulence intensity and scale as well as mean velocities. For each experiment, capture efficiency will be measured as a function of distance from the hood while holding hood length, hood width, hood face velocity, crossdraft velocity, and turbulence intensity and scale constant. The results will be used to develop a model for capture efficiency.

Significant Findings

The first part of the project is complete. Velocity and turbulence characteristics have been determined for the four experimental conditions outlined above. These will be used to design experiments to measure dispersion of contaminants as a function of turbulence intensity and scale. A wind tunnel is currently being built in the laboratory and the experiments will begin in January 1991.

New Methods for Quantitative Respirator Fit Testing

Klaus Willeke, Ph.D., CIH
University of Cincinnati
College of Medicine
Department of Environmental Health
3223 Eden Avenue
Cincinnati, Ohio 45267-0056

Program Area: *Respirator Research*
Grant Number: *2 R01 OH01301-07*
Start & End Dates: *09/29/82 - 08/31/92*
Funding Level: *$151,077 ($840,369 Cum)*

Importance to Occupational Safety and Health

Several million air purifying respirators are in use in the U.S. A significant percentage of the American workforce is, therefore relying on respirators to reduce the risk of inhaling hazardous industrial aerosols. OSHA guidelines specify respirator fit testing to ensure the workers' safety. Field studies have shown that the laboratory-measured quantitative fit factors relate poorly or not at all to the workplace protection measured during work performance. Fast, reliable, and low-cost fit testing techniques are needed to ensure that the chosen respirator provides adequate protection.

Objectives

The overall aim of this research is to study the basic mechanisms of air and aerosol penetration through face seal leaks and the filtering material, and to develop from this knowledge quantitative fit tests that are easy and inexpensive to perform. Two types of respirators in common use are studied: (1) disposable respirators which consist mostly or entirely of contoured filtering material and (2) half-mask respirators which have air purifying cartridges attached to an impermeable body of rubber or silicone.

Methodology

For the disposable respirator research, a size-fractionating aerosol generator has been developed which can deliver a high fraction of large particles and a low fraction of small particles so that a statistically significant number of particles is sampled from inside the respirator cavity over a wide range of particle sizes. The particle size distributions are measured by a computer-based aerosol size spectrometer. For the half-mask respirators, pressure sensing attachments have been developed through which the face seal leak flow rate is determined. A field computer determines the fit factor. The new method is tested on respirators in actual use and is compared with available methods used on surrogate respirators.

Significant Findings

Through use of a condensation nuclei counting technique for fit testing respirators, the traditional aerosol generator and exposure tent or booth are no longer needed. This simplification and cost reduction has increased the use of quantitative fit testing. The dynamic pressure testing technique (still under development) is further reducing the cost and making fit testing available for use on the actual respirator worn in the field. The new size-fractionating aerosol generator and a low-loss sampling probe and train provide the basic tools for measuring the significant characteristics of disposable respirators. Measurements of the filter penetration characteristics have shown that the protection provided by a given class of respirator may differ significantly from one manufacturer to another. From these data, new techniques suitable for disposable respirators will be developed.

Publications

Xu M, Han D, Hangal S, Willeke K: Respirator Fit and Protection through Determination of Air and Particle Leakage. Annals of Occupational Hygiene, accepted, 1990

Chen CC, Ruuskanen J, Pilacinski W, Willeke K: Filter and Leak Penetration Characteristics of a Dust and Mist Filtering Facepiece. American Industrial Association Journal, in press, 1990

Xu M, Chen CC, Han D, Pilacinski W, Szewczyk K, Lehtimäki M, Krishnan U, Brueck S, Hangal S, Willeke K: Protection from Aerosols through Respirator Wear. In: Aerosols: Science, Industry, Health, and Environment, (eds. S Masuda, K Takahashi), Pergamon Press, Oxford, Vol 2, pp 864-867, 1990

Willeke W, Krishnan U: Present Procedures in Quantitative Respirator Fit Testing: Problems and Potential Solutions. Applied Occupational and Environment Hygiene 5:762-765, 1990

Pilacinski W, Szewczyk K, Lehtimäki M, Willeke W: Characteristics of a Double-Orifice Nebulizer. Journal of Aerosol Science 21:977-982, 1990

Pilacinski W, Chen CC, Ruuskanen J, Pan M, Willeke K: Size Fractionating Aerosol Generator. Aerosol Science and Technology 13:450-458, 1990

Willeke K, Xu M, Han D, Foo SC, Hangal S: Determination of Aerosol Penetration into Respirators. Proc of American Association for Aerosol Research, Reno, NV, 1989

Chen CC, Pilacinski W, Ruuskanen J, Pan M, Willeke K: Aerosol Penetration Characteristics in Disposable Respirator Wear. Proc of American Association for Aerosol Research, Reno, NV, 1989

Ruuskanen J, Chen CC, Carpenter DR, Sherman A, Willeke K: Aerosol Penetration Characteristics for Disposable Respirator Facepieces. J Aerosol Science 19:1445-1448, 1988

Carpenter DR, Willeke K: Non-invasive, Quantitative Respirator Fit Testing through Dynamic Pressure Measurement. Am Ind Hygiene Assoc J 49:485-491, 1988

Carpenter DR, Willeke K: Quantitative Respirator Fit Testing: Dynamic Pressure versus Aerosol Measurement. Am Ind Hygiene Assoc J 49:492-496, 1988

Holton PM, Tackett DL, Willeke K: Particle Size-Dependent Leakage and Losses of Aerosols in Respirators. Am Indus Hyg Assoc J 48:848-854, 1987

Holton PM, Willeke K: The Effect of Aerosol Size Distribution and Measurement Method on Respirator Fit. Am Ind Hygiene Assoc J 48:855-860, 1987

Respirator Performance Model for Particulates

William C. Hinds, Sc.D.
University of California, Los Angeles
School of Public Health
405 Hilgard Avenue
Los Angeles, California 90024

Program Area: *Respirator Research*
Grant Number: *5 R01 OH01595-06*
Start & End Dates: *04/01/88 - 08/31/91*
Funding Level: *$94,391 ($430,985 Cum)*

Importance to Occupational Safety and Health

The ability of airborne particles to penetrate the filters, exhalation valves, 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 obtained for airborne particles will depend on the particle sizes present in the workplace environment. This study characterizes the effect of particle size distribution on the performance of representative single-use, half-mask, and full-face mask respirators. No general data exist to describe the performance of respirators as a function of particle size distribution. These projects will improve, extend, and validate the use of the computer model for characterizing and predicting respirator wearer's exposure. It is anticipated that when the model is fully developed, it will be a useful tool for respirator research and a useful screening tool for respiratory protection programs.

Objectives

The overall objective of this grant is to extend our understanding of the effect of particle size on the performance of air-purifying respirators for protection against particulate exposures. This is accomplished through experimental measurement of filter, exhalation valve, and facial seal leak performance as a function of particle size and flowrate and the use of these data in a computer model to predict overall performance for a respirator based on QNFT measured leakage, airborne particle size distribution, and the work rate of the wearer.

The specific projects are: (1) To evaluate leakage of normal and impaired exhalation valves during inhalation. (2) To perform model validation

measurements with human subjects wearing respirators. (3) To evaluate the performance of respirator filters as they become loaded with dust. (4) To evaluate the penetration characteristics of facial seal leaks for full-face masks.

Methodology

Projects 1, 3, and 4 are performed using the laboratory test apparatus described in AIHAJ, 48, 836 (1987). Masks are mounted on a manikin and penetration or leakage is evaluated with an oleic acid test aerosol over the particle size range of 0.1 to 11 μm. In Project 1, monodisperse aerosols containing a fluorescent dye are used and flow is established with a breathing machine. Projects 3 and 4 use polydisperse aerosols under steady flow conditions. Penetration is measured with an optical particle counter or aerodynamic particle sizer. Project 2 will use human subjects. Facial seal leakage will be measured with a quantitative fit testing apparatus. A polydisperse oleic acid test aerosol with a fluorescent tag will be used. Concentration will be measured inside and outside the mask and compared to that predicted by the model.

Significant Findings

The initial phase of this study included detailed laboratory evaluations of respirator filter performance as a function of particle size and flowrate, and penetration of particles through facial seal leaks as a function of particle size and pressure drop.

The evaluation of exhalation valves is complete. Leakage for clean valves ranges from less than 0.001 to .05%, increasing with work rate. A 0.1 mm foreign object on the value seat can increase valve leakage by 2 to 3 orders of magnitude to about 1%.

The detailed data bases that we have developed are used in a computer model that predicts overall respirator performance for any particle size distribution, work rate, and fit for a given half mask respirator and filter.

Analysis using the model shows that the protection provided in the workplace by a given respirator and fit may vary 20-fold for the usual range of particle size distributions found in work environments.

An analysis of the effect of respirator dead space on averaged inhaled concentration concluded that the use of peak inhalation concentration in QNFT may overestimate average inhaled concentration by up to 35%. Use of full-cycle average measurements in WPF studies may underestimate average inhaled concentration by as much as 50%. Protection factors calculated by the computer model may overestimate by 45% inhaled dose for half masks and by 90% for full-face masks.

A literature search on the effect of dust loading on filter efficiency and pressure drop has been completed. These data have been summarized in the form of an empirical predictive equation.

The experimental set-up for the human subject model validation tests has been completed and preliminary tests are underway.

Publications

Bellin P, Hinds WC: Aerosol Penetration Through Respirator Exhalation Valves. Am Ind Hyg Assoc J 51:555-560, 1990

Hinds WC, Bellin P: Effect of Facial-Seal Leaks on Protection Provided by Half-Mask Respirators. Appl Ind Hyg 3:158-164, 1988

Hinds WC, Kraske G: Performance of Dust Respirators with Facial-Seal Leaks: I. Experimental. Am Ind Hyg Assoc J 48:836-841, 1987

Hinds WC, Bellin P: Performance of Dust Respirators with Facial-Seal Leaks: II. Predictive Model. Am Ind Hyg Assoc J 48:842-847, 1987

Hinds WC, Kraske G: A Bench-Scale Aerosol Test Chamber. Appl Ind Hyg 2:13-17, 1987

Hinds WC, Kraske G: Performance of PMS Model LAS-X Optical Particle Counter. J of Aerosol Science 17:67-72, 1986

Hinds WC, Kraske G: Performance of PMS Model LAS-X Optical Particle Counter (extended abstract) in Aerosols: Science, Technology and Industrial Application of Airborne Particles. (eds. Liu, Pui, Fissan), p 31-34, Elsevier, New York. Presented at First International Aerosol Conference Minneapolis, MN, September 17-21, 1984

Measure of Work Performance Decrement Due to Respirators

Neil J. Zimmerman, Ph.D.
Purdue University
Department of Medical Chemistry and Pharmacognosy and School of Health Sciences
W. Lafayette, Indiana 47907

Program Area: *Respirator Research*
Grant Number: *5 R01 OH01632-02*
Start & End Dates: *03/01/87 - 10/31/89*
Funding Level: *$123,194 ($257,441 Cum)*

Importance to Occupational Safety and Health

The ability to quantitatively identify a decrement in work performance due to respirators is important to estimate the economic impact of such an effect as well as to evaluate differences in respirator design. Although this study was not able to make major distinctions between different types of respirators, a method to effectively measure work decrement was identified. Follow-up studies are needed to validate the results and compare them to effects seen in actual workplaces.

Objectives

The specific aim of this project was to develop a generalized test procedure or measurement technique which could be used to determine quantitatively the decrement in worker performance resulting from the wearing of various respirators. The hypotheses of the project, thus, were that there is a measurable decrement in work performance caused by the wearing of a respirator, and that the amount of decrement will vary with factors attributable to each respirator.

Methodology

These hypotheses have been examined by observing subjects' performances at three different levels of simulated work tasks while wearing one of three different types of respirators or no respirator as a control. A homogeneous panel of twelve young, healthy, non-smoking, adult male volunteers was selected. The three levels of work tasks, (1) cognitive, or decision making, (2) psychomotor, or manual dexterity skills, and (3) moderate physical work (bicycle ergometer), were selected to represent a wide range of tasks. The three types of respirators, (1) a disposable dust filter mask, (2) a half-mask with high efficiency filter cartridges, and (3) a full-facepiece air line respirator with pressure demand flow, were selected to represent the most widely used types of respirators in industry. The performance criteria to be used for evaluation were, respectively by task, (1) test score, (2) skill score, and (3) oxygen consumption, as a measure of exertion.

Significant Findings

The results from the physical work task indicated approximately a 10% increase in oxygen consumption with the half and full-face masks. This supports previous physiological findings and suggests that respirators can be an additive factor that will contribute to work performance decrement. The effect of respirators on cognitive task performance are important, but difficult to evaluate. Considering the bias of the different difficulty levels of the tests used in the experiment, the results indicate that the 5 respirators did not appear to affect the performance of cognitive tasks. The psychomotor task test methods appear to be the best indicators of respiratory effects on work performance decrement. A steadiness task showed a 31% decrement for the full-face respirator. The one-hole test, which includes a number of sub-tests which can be evaluated, indicated an average movement time decrement of 16%. The other one-hole test indicators also showed decrements, but were lower and not statistically significant.

In summary, this research has:

1. Documented a statistically and potentially economically significant decrement in work performance due to the wearing of respirators.
2. Identified a psychomotor manual dexterity test instrument that can detect these decrements in work performance due to respirators, although it could not differentiate between respirators.

Publications

Zimmerman NJ, Eberts C, Salvendy G, McCabe G: Effects of Respirators on Performance of Cognitive, Psychomotor and Physical Tasks. Ergonomics, in press, 1991

Zimmerman NJ, Eberts C, Salvendy G, McCabe G: Measure of Work Performance Decrement Due to Respirators. Proc of 1990 Human Factors Society 34th Annual Conference, Orlando, Florida, October 8-12, 1990

Respirator Tolerance

Philip I. Harber, M.D., M.P.H.
University of California, Los Angeles
Occupational Medicine Branch
Department of Medicine, UCLA
Los Angeles, California 90024-1690

Program Area: *Respirator Research*
Grant Number: *5 R01 OH02005-06*
Start & End Dates: *09/16/87 - 03/31/91*
Funding Level: *$76,720 ($573,602 Cum)*

Importance to Occupational Safety and Health

Respirators can be a very effective preventive measure, but they must be as free of adverse effects as possible to encourage their use and avoid direct interference with work ability. Understanding the physiologic and psychologic effects of respirators will facilitate improved design, proper equipment certification methods, and medical evaluation of workers for respirator use.

Objectives

This project evaluates the physiologic and subjective responses to respirator use. The project will identify and quantitate the major loads imposed by different respirators and develop improved methods to test respirators.

Methodology

Respirator effects are being assessed using actual respirators. Measurements include ventilatory parameters, selected respiratory control parameters, subjective response, and psychophysiologic sensitivity to added loads. Studies are performed in controlled laboratory settings, under field conditions, and on site at industrial facilities. Measurements are repeated over time to assess stability of responses.

Significant Findings

The physiologic response to each type of respirator was evaluated, including flow resistance (inspiratory and expiratory), dead space, and pressure biasing. Nasal-oral flow partitioning and absolute resting lung volume changes (FRC) were also measured. Subsequently, subjective response was also determined. Inspiratory flow resistance is more important than dead space loading. Pressure bias, as with pressure demand respirators, is also important both physiologically and subjectively.

The respirator effect on adaptation of respiratory control (to optimize work of breathing or to minimize sensation) was as important as total ventilation. Further studies showed that respiratory pattern adaptation is consistent across subjects and across levels of exercise; in addition, respiratory impaired workers show a consistent response for these variables. Subjective response also correlates with respiratory timing adaptation. Thus, effects on respiratory pattern seem particularly useful for evaluating workers and respirators. Ventilation limitation alone does not explain respirator tolerance at submaximal exercise levels.

The studies of normal volunteers in the laboratory setting were complemented by studies of impaired subjects and by studies on site in two industrial facilities. Respiratory inductive plethysmography (RIP) was applied, allowing measurement with actual unmodified respirators and in field activities, which are more similar to real life use.

Personal factors affecting tolerance were also studied. Psychophysical load scaling sensitivity (LSS) is an objectively measured personal characteristic, describing growth of sensation with added resistances. An individual's LSS helps determine pattern of breathing response and subjective response. Furthermore, on the average, LSS declines with respirator use, thereby improving tolerance to the imposed load. Differences in LSS (and consequent maladaptation of respiratory pattern) may partially explain differences in tolerance. A group of industrial users self-classified themselves as tolerant/intolerant; there was a tendency for differences to persist on each subjective subscale and for the intolerants to have a higher LSS.

Subjective measures may be consistently measured, are related to physiologic response, and reflect two important personal characteristics (LSS and self-rated tolerance). They can distinguish respirator load types and provide complementary information to physiologic measures. The components of subjective response were assessed. The data suggest that subjective response should be included in evaluations of both respirator designs and specific workers.

Extensive studies showed general comparability of volunteer, mildly impaired, and industrial populations. Field course testing showed results comparable to those of the laboratory and was surprisingly consistent.

In summary, the project has shown that respirator effects cannot be considered simply as

limiting ventilation and maximal exercise. Important respiratory control adaptation and subjective effects were described, and the project evaluated interrelationships among various respirator loads, exercise level, personal characteristics, ventilatory, sensation, respiratory control, and subjective effects. These factors should be considered when comparing alternative respirators or testing workers. They also explain why some apparently "normal" workers have poor tolerance.

Publications

Harber P, Brown C, Beck J: Respirator Physiology Research: Answers in Search of the Question. J Occup Med, in press, 1991

Harber P, Luo J, Beck J, Brown C: Role of Subjective Response in Evaluating Respirators. Am Rev Respir Dis 141:A594, 1990 (Abstract)

Harber P, Shimozaki S, Barrett T, Loisides P, Fine G: Effects of Respirator Dead Space, Inspiratory Resistance, and Expiratory Resistance Ventilatory Loads. Amer J of Ind Med 16:189-198, 1989

Harber P, Shimozaki S, Barrett T, Loisides P, Fine G: Effects of Exercise Level on Ventilatory Adaptation to Respirator Use. J Occup Med 32:1042-1046, 1989

Harber P, Barrett T, Shimozaki S, Kanter R: Respirator Effect in Pulmonary Impaired Subjects. Am Rev Respir Dis 139:A491, 1989

Harber P, Lew M, Shimozaki S, Thomas B: Non-Invasive Measurement of Respirator Effect at Rest and During Exercise. Am Ind Hyg Assoc J 50:428-433, 1989

Harber P, Shimozaki S, Barrett T, Loisides P: Relationship of Subjective Tolerance of Respirator Loads to Physiologic Effects and Psychophysical Load Sensitivity. J Occup Med 31(8):681-86, 1989

Harber P, SooHoo K, Lew M: Effects of Industrial Respirators on Respiratory Timing and Load Sensitivity. J Occup Med 30:257-262, 1988

Shimozaki S, Harber P, Barrett T, Loisides P: Subjective Tolerance of Respirator Loads and Its Relationships to Physiologic Effects. Am Ind Hyg Assoc J 49:108-116, 1988

Harber P, Shimozaki S, Barrett T, Fine G: Determination of Pattern of Breathing During Respirator Use. Am J Indust Med 13:253-262, 1988

Harber P: Respirator Use in the Work Environment. Am Rev Respir Dis 138 1048-1051, 1988

Harber P: Physical Standards for Job Placement. Practice of Occupational Medicine, (ed. R McCunney), Little Brown, Boston, pp 401-409, 1988

Harber P: Medical Considerations of Placement of the Respiratory Impaired Worker. Occup Med-State of Arts Revs 3:285-298, 1988

Harber P, Shimozaki S, Barrett T, Fine G: Effect of Exercise Level on Ventilatory Adaptation to Respirator Use. Am Rev Respir Dis 137:300S, 1988 (Abstract)

Harber P: The Evaluation of Pulmonary Fitness and Risk. Occup Med 3:285-298, 1988

Harber P, Shimozaki S, Barrett T, Loisides P: Subjective Tolerance of Industrial Respirators: Effects of Resistive and Dead Space Loads. Chest 92:149S, 1987 (Abstract)

Harber P, Shimozaki S, Barrett T, Fine G: Interaction of Physiologic, Psychophysical, and Subjective Factors. Am Rev Resp Dis 135:A19, 1987 (Abstract)

Harber P: Use of Personal Respiratory Protective Devices (Respirators). West J Med, 1985

Harber P: Alternative Partial Respiratory Disability Evaluation Systems. J Occup Med 27:675-676, 1985

Respiratory and Thermal Physiology of Face Masks

Arthur B. DuBois, M.D.
John B. Pierce Foundation Laboratory
290 Congress Avenue
New Haven, Connecticut 06519

Program Area: *Respirator Research*
Grant Number: *5 R01 OH02564-03*
Start & End Dates: *05/01/88 - 04/30/91*
Funding Level: *$141,912 ($396,175 Cum)*

Importance to Occupational Safety and Health

When workers who are unavoidably exposed to dusts, fumes, or noxious gases in the workplace wear appropriate respiratory protective devices correctly, they avoid the potentially harmful effects on the lungs of exposure to such substances. Though well designed, carefully manufactured, and thoroughly tested, such devices are implicitly uncomfortable to wear and produce some inconvenience or interference with the accomplishment of the task to be performed by the worker. Experience has shown that despite their need in appropriate circumstances, such devices may not be put on by the worker. Any improvement in the comfort of respiratory protective devices would be highly desirable because it would eliminate an obstacle that prevents workers from wearing them.

Objectives

The overall objective of this study is to pinpoint and eliminate the factors that cause discomfort of respiratory protective devices. To remove the source of the discomfort, it is necessary to know its cause. Studies supported by this grant have shown that the air in face masks is hot and humid, that the skin temperature of the wearer's face increases, and that the unaccustomed warmth of the face is accompanied by discomfort which is reduced when the air around the face is cool and dry. The resulting hypothesis has been that the dominant factors contributing to discomfort of respiratory protective devices are the elevation of temperature of the skin of the face and skin wetness due either to sweating or condensation of water vapor on the face.

Current objectives are to evaluate thermal discomfort in relation to other sources of discomfort and inconvenience of respiratory protective devices, to decrease thermal discomfort to a minimum by modification of face masks to remove heat from the mask, and to diminish re-inspiration of heat and moisture accompanying either tidal breathing or delivery of a continuous air supply.

Methodology

Psychophysical ratings and skin temperature of the face were measured. A dummy mask was constructed of aluminum and its walls cooled by evaporation of water from a cotton cloth adherent to its outer surface. The comfort and skin temperature obtained on subjects wearing this cool mask were compared with those of the same subjects wearing a nuisance dust mask (3-M 9913 Dust-Mist) and a rubber mask which had inspiratory valves with cannister filters and an expiratory flap valve (Willson model 122510). Sensations of comfort, warmth, and skin wetness were plotted as a function of skin temperature on the face of the subject, and the regression lines were compared with those obtained previously using a flow-through air supply.

An existing half-facepiece (Scott twin cartridge respirator model 66) has been modified and tested. To cool it, we cut four 3 X 5 cm pads from a 2 mm thick sheet of felt, sprayed the backs of the pads with a detachable adhesive (Scotch/3M Brand Spray Mount Artist's Adhesive) similar to that used for "Post-it" notes, and attached the felt pads to the cheek and chin regions of the central plastic shell of the mask. Thermocouples were attached to the nasolabial fold, the inner wall of the mask, and the outer wall of the mask. Comfort votes were recorded at appropriate intervals. Five subjects wore the mask with the pads dry, then wet, during 30-minute intervals at rest, or 20-minute periods of exercise on a bicycle ergometer set for a work output rate of 60 watts.

Significant Findings

The most significant finding from comparison of the Willson, 3-M, and aluminum wet masks was that skin temperatures of the face above 34.5°C were uncomfortable. The ratings of warmth, wetness, and comfort of the three masks that required tidal airflow were identical to the ratings at corresponding values of skin temperature when using the flow-through air delivery system. Yet the weight, configuration, deadspace, observers, recording equipment, and subjects were different. This means that the dominant factor was the influence of air in front of the face on temperature and wetness of the skin of the face. The aluminum

mask that was cooled by evaporation of water from its outer surface was rated "comfortable."

Before putting on the Scott Mask modified with pads, resting subjects had a mean skin temperature of the face of 33.6°C. Wearing the dry mask, the face temperature increased to 34.7°C. The temperature inside the mask wall was 31.2°C. The face felt slightly uncomfortable, slightly warm, and slightly humid. When the felt pads were wet, the face was 34.0°C, temperature inside the mask wall was 29.1°C, and the discomfort, thermal sensation, and sense of humidity were reduced. The sensations were in keeping with those previously found at corresponding skin temperatures when wearing other face masks.

Before putting on the modified Scott mask, exercising subjects had face temperatures of 33.3°C. After twenty minutes of moderate bicycle exercise wearing the dry mask, the temperature of the skin of the face was again 33.3°C, and the inner mask wall temperature was 30.3°C. The face felt slightly uncomfortable, slightly to moderately warm, and slightly wet. When the felt pads were wet, the face was 32.8°C, and mask wall 28.1°C. The face again felt slightly warm, slightly uncomfortable, and slightly to moderately wet. The inside of the mask was cool (28.1°C) and dry (we know it was dry because we wiped it with Kimwipes and found that the paper had not increased in weight). We deduced that the large volume rate of respiratory airflow during exercise was causing evaporation of water which had condensed inside the mask wall, as well as evaporation of water from the skin of the subjects' faces.

Further steps to be taken in cooling a mask will include changing the wall to a heat conductive material, cooling a larger fraction of the surface by evaporation, and modification of the breathing valves to carry away more hot moist expired air to avoid re-inspiration with the next breath.

Publications

DuBois AB, Harb ZF, Fox SH: Thermal Discomfort of Respiratory Protective Devices. Am Ind Hyg Assoc J 51(10):550-554, 1990

Gwosdow AR, Nielsen R, Berglund LG, DuBois AB, Tremml PG: Effect of Thermal Conditions on the Acceptability of Respiratory Protective Devices by Humans at Rest. Am Ind Hyg Assoc J 50:188-195, 1989

Nielsen R, Berglund LG, Gwosdow AR, DuBois AB: Thermal Sensation of the Body as Influenced by the Thermal Microclimate in a Face Mask. Ergonomics 30(12):1689-1703, 1987

Nielsen R, Gwosdow AR, Berglund LG, Dubois AB: The Effect of Temperature and Humidity Levels in a Protective Mask on User Acceptability During Exercise. Am Ind Hyg Assoc J 48(7):639-645, 1987

Quantitative Respirator Fit Test by Negative Pressure

Clifton D. Crutchfield, Ph.D.
The University of Arizona
School of Health Related Professions
1435 N. Fremont
Tucson, Arizona 85719

Program Area: *Respirator Research*
Grant Number: *5 K01 OH00068-03*
Start & End Dates: *08/01/87 - 07/31/90*
Funding Level: *$32,344 ($97,144 Cum)*

Importance to Occupational Safety and Health

Development of a respirator fit test method that is based on directly measuring air leakage into respirators will provide a more universally applicable predictor of actual respirator performance. The controlled negative pressure (CNP) method is independent of the aerosol loss and mixing problems that significantly bias results produced by the current standard method of respirator fit testing.

Objectives

The principal objective was to investigate the capabilities of a new quantitative respirator fit test method based on CNP. The CNP method is based on exhausting air from a temporarily sealed mask, thereby generating a negative pressure that replicates the inspiratory driving force for leakage into the mask. The exhaust flow rate that is required to generate and sustain a pre-selected negative pressure in the mask is a direct measure of the mask leakage flow rate, which can be used as an index of respirator fit.

Phase II objectives included defining inspiratory pressures and flow rates for various air purifying media over a range of metabolic work rates. This information can be utilized to make fit testing more representative by making it work-rate dependent.

A number of problems involving aerosol losses were observed while using an aerosol fit test

method as a comparison standard. The research focus during Phase 3 was on developing a method to determine respirator protection factors that is independent of the biases introduced by the use of aerosols. A method based on using a vapor challenge agent and biological sampling of breath was developed and pilot tested with a single subject.

Methodology

Sensitivity and precision limits of the CNP quantitative fit test method were determined in a sequential comparison study using a computerized aerosol fit test system as a comparison standard. A test population recruited from Air Force personnel already assigned to a respiratory protection program was used.

Capabilities of the new method to measure respirator fit over a range of non-rest work rates was examined with a computerized open-circuit spirometric technique. A bicycle ergometer was used to set and maintain 4 different work rates, and inspiratory pressures and flow rates were measured for both male and female subjects wearing half- and full-face air purifying respirators equipped with low, medium, and high resistance cartridges.

Significant Findings

Phase 1

1. Measurements of a series of fixed leaks (no human subjects involved) made with the CNP fit test system and the standard aerosol fit test system were highly correlated.
2. Consistent fit test results could be achieved with the CNP system during tests of approximately 10 seconds duration.
3. CNP results were not affected by the aerosol depositional losses in the fixed leak needles that were evident in the aerosol system data.
4. Sequential respirator fit tests made on human subjects with both systems showed that CNP results were consistently more conservative and less variable than aerosol results. The order of magnitude differences in the results were attributed to aerosol test biases including penetration losses, poor mixing, streamlining, and lung deposition that have also been observed by other investigators.

Phase 2

1. The inspiratory pressure in an air-purifying respirator is primarily dependent upon work rate and purifying cartridge resistance. Mask type and gender were also found to have a significant impact upon inspiratory pressure.
2. A series of linear equations can be used to predict inspiratory pressure as a function of work rate, cartridge resistance, mask type, and gender. Using the predicted inspiratory pressure as the challenge pressure for the CNP system allows work-rate dependent quantitative respirator fit testing.

Phase 3

1. Biological breath sampling provides a means of determining respirator protection levels that is independent of in-mask sampling biases. A protection factor range of 10 to 1000 can be reproducibly covered using a fluorocarbon vapor challenge agent and a GC/electron capture analytical method.
2. Comparison of respirator leak measurements made with the CNP fit test system and the breath sampling method yielded a correlation coefficient of 0.86. If verified by a full-scale study, this finding indicates that the CNP method may be a better predictor of respirator performance under work conditions. The negative pressure system, which is non-invasive, proved to be a more sensitive detector of respirator leaks than the aerosol system. It also consistently exhibited less system variation and produced more conservative measures of respirator fit than the aerosol system.

Publications

Crutchfield CD, Murphy RW, Van Ert MD: A Comparison of Controlled Negative Pressure and Aerosol Quantitative Respirator Fit Test Systems Using Fixed Leaks. American Industrial Hygiene Association Journal, in press, 1990

Crutchfield CD, Murphy RW, Van Ert MD: Evidence of Significant Aerosol Loss and Consequent Overestimation of Fit During Quantitative Respirator Fit Testing. American Industrial Hygiene Association Journal, in press, 1990

Factors Affecting Respirator Leak Sites and Shapes

Riedar K. Oestenstad, Ph.D.
University of Alabama at Birmingham
School of Public Health
Department of Environmental Health Sciences
UAB Station
Birmingham, Alabama 35294

Program Area: *Respirator Research*
Grant Number: *1 K01 OH00085-01A1*
Start & End Dates: *09/28/90 - 09/27/93*
Funding Level: *$53,138 ($53,138 Cum)*

Importance to Occupational Safety and Health

Results of this study will expand our knowledge of where respirator faceseals leak, how leak sites are related to such critical factors as facial dimensions and the brand of respirator, and whether leak sites vary between different fittings and fit test exercises. This information will be useful to persons designing respirator facepieces and to those responsible for selecting and testing respirators for individual users. It will permit more accurate modelling of respirator leakage by determining the size and one-dimensional shape of faceseal leaks on human subjects. The study will also provide additional information on the phenomenon of airflow streamlining inside respirator facepieces.

Objectives

The specific objectives of the study are to: (1) determine if leak sites and shapes change between the exercises of a quantitative fit test, (2) determine the variation of leak sites and shapes for multiple fittings of the same respirator on the same subject, (3) determine the distribution of leak sites and shapes for different respirators being worn by the same sample of subjects, (4) more accurately define the characteristics of subjects who show evidence of aerodynamic streamlining under the respirator facepiece, and (5) determine the effect of increased breathing rates on the development of airflow streamlining patterns.

Methodology

The first four objectives will be accomplished by performing respirator fit tests on human subjects using an aerosol of a fluorescent whitening agent. Faceseal leak sites will be identified by observation of fluorescence of the aerosol deposited at the site(s) when illuminated by ultraviolet light. The one-dimensional width of observed leaks will be measured and their site categorized by facial location. Anthropometric facial dimensions of the subjects will also be measured. The fifth objective will be accomplished by performing the same tests on a mannequin fitted with a respirator using a breathing simulator. Data will be analyzed by conditional logistic regression, multiple linear regression, and ANOVA.

Significant Findings

None to date.

Adsorption of Vapor Mixtures onto Activated Carbon

Patrick N. Breysse, Ph.D.
The Johns Hopkins University
School of Hygiene and Public Health
Department of Environmental Health Sciences
615 North Wolfe Street
Baltimore, Maryland 21205

Program Area: *Respirator Research*
Grant Number: *1 K01 OH00087-01*
Start & End Dates: *09/28/90 - 09/27/93*
Funding Level: *$54,000 ($54,000 Cum)*

Importance to Occupational Safety and Health

Complex industrial environments typically contain numerous organic vapors and a range of relative humidities. It is not possible to experimentally determine respirator breakthrough performance for every possible combination of vapor mixtures. A fundamental understanding of the physicochemical interaction of adsorption of vapor mixtures is needed in order to properly model activated carbon bed behavior. Data generated by this proposal will be used to evaluate and modify existing respirator service-life models.

Objectives

The purpose of these investigations is to evaluate adsorption of organic vapor mixtures onto activated carbon. Experiments are designed to

evaluate adsorption equilibria and kinetics. Binary vapor mixtures containing a variety of different polarities and functional groups at different humidities will be evaluated.

Adsorption studies using silica gel are also to be conducted. Adsorption onto silica gel, a polar adsorbent, will help to determine the role of polar forces in adsorption and to evaluate the suitability of silica gel as an adsorbent.

Successful completion of this project will provide a more fundamental understanding of adsorption of complex organic vapor mixtures onto activated carbon and silica gel.

Methodology

Experimental data will be analyzed using parameters of the Dubinin equilibrium model and the Wheeler kinetic model. These parameters include equilibrium adsorption affinity coefficients and capacities and kinetic rate constants and capacities. Equilibrium and kinetic behavior of vapor mixtures will be evaluated using gas chromatography (GC). Mixed vapor analysis will be conducted using two different GC detectors, one which is sensitive to only one of the vapors in the mixture.

Significant Findings

None to date.

An Advanced Respiratory Protective Device

Joseph R. Stetter, Ph.D.
Transducer Research, Inc.
1228 Olympus Drive
Naperville, Illinois 60540

Program Area: *Respirator Research*
Grant Number: *5 R44 OH02312-03*
Start & End Dates: *09/15/88 – 03/31/91*
Funding Level: *$199,843 ($448,419 Cum)*

Importance to Occupational Safety and Health

Air purifying respirator cartridges are used to allow workers to remain in an ambient environment which contains toxic gases that would be harmful to breathe. Depending on the concentration of the toxic gas and other factors, respirator cartridges may last from minutes to days before they are expended. One of the major problems users face is determining when the cartridge service life has ended. An active-end-of-service-life indicator (AESLI), that is being developed under this grant, would be placed in the adsorbent bed and would signal the user when the cartridge life is nearing the end.

The presence of an unambiguous signal to warn the user that the cartridge is almost expended would give greater protection to the user, who would not have to rely on sensory indicators such as smell. In addition, the AESLI could be used for toxic gases for which there is no sensory warning, regulations permitting. This could lead to the use of air–purifying respirators with many compounds which now require the use of a SCBA (self-contained breathing apparatus). The use of simpler respirators rather than SCBA in the workplace will lower operating costs, as well as improve worker comfort and efficiency.

The development of AESLI is of especially great significance today since the TLV's of about 500 compounds have been lowered, and adequate sensory warning is not provided at these reduced levels for many compounds. When an AESLI is available, it will be possible to continue to employ air purifying respirators instead of self-contained breathing apparatus (SCBA) in many applications.

Objectives

The major objective of this research is the development of AESLIs. The AESLIs must provide an unambiguous alarm to the user when at least 10% of the respirator cartridge life remains unused, and the AESLIs cannot interfere with the operation of the respirator.

Methodology

Microchemical sensors that operate on ultra low power and detect ppm levels of chemical vapors and gases are applied to the problem of detecting toxic vapors inside an active adsorbent bed. The techniques of chemiresistor, fiber optic, electrochemical, and piezoelectric micro-sensors are being investigated. The approach is to interface the new micro-sensor technology with existing adsorbent-based protection systems to create prototype respiratory protection devices that can protect the user and alert/alarm when the adsorbent is spent and the protection is not adequate. The sensors are being developed and interfaced to existing respiratory equipment. Both the sensors and the systems are being evaluated for their intended purpose under laboratory conditions

that characterize performance and simulate field conditions.

Significant Findings

1. Low power carbon-based chemiresistor sensors that operate at adsorbent bed temperatures have been developed. The sensitivity of the sensors has been improved to about 100 ppm for many organic compound vapors. This type of device has been incorporated into carbon beds, and is currently being tested. A joint test at the NIOSH respirator certification facility in Morgantown, WV is planned, if possible.

   Research into the sensor mechanism has been performed, and a basic model for the response of the device proposed. Efforts to improve the sensitivity of the device even further are focused on increasing the stability of the ambient resistance with temperature and RH fluctuations by compensating for variation, and identification of a polymer matrix with a smaller response to water vapor.
2. Colorimetric indicators have been designed and tested for detection of acid gas vapors. The size and power requirements of fiber optic based devices make the approach amenable to AESLI applications. Gases which can be detected by this technique include HF, HCl, and other acid vapors.
3. Electrochemical detectors for CO and H_2S have been mounted in respirator equipment and used in field applications, specifically forest fire fighting. The further advantage of such sensors is that they can be placed "in mask" and alarm not only when the cartridge fails but also when the equipment leaks. The sensitivity of this type of sensor to analyte gases (10-100 ppb detection limit) allows placement in-line after the canister while offering ample protection to the wearer.

Publications

Maclay GC, Yue C, Findlay MW, Stetter JR: An Active-End-of-Service-Life Indicator for Respirator Cartridges. Applied Occupational and Environmental Hygiene, in press, 1990

Maclay GC, Yue C, Findlay MW, Stetter JR: An Active-End-of-Service-Life Indicator for Respirator Cartridges. Proceedings of the American Industrial Hygiene Conference, Orlando, FL, May 13-17, 1990

Development of Novel Sorbents for Respirators

Bruce L. Roberts
Surfactant Associates, Inc.
P.O. Box 2705
Norman, Oklahoma 73070

Program Area: *Respirator Research*
Grant Number: *1 R43 OH02698-01*
Start & End Dates: *09/30/89 – 03/29/90*
Funding Level: *$46,820 ($46,820 Cum)*

Importance to Occupational Safety and Health

The adsorbent in industrial respirator cartridges is activated carbon. At low relative humidities, water vapor has little effect on the adsorption of most organics in respirator cartridges. However, at a critical relative humidity (usually 50 - 60%), water vapor can substantially reduce both the effective and equilibrium capacity for organics. This is due to capillary condensation of water in micropores in the activated carbon. In dry air, the cartridges are effective in removing non-polar organics of molecular weight above 100. However, current chemical cartridges can be very ineffective at removing volatile, polar organics, such as ethylene oxide or vinyl chloride. The desired result of this project would be an "all purpose chemical cartridge," useful for a wide variety of toxic gases over a wide range of relative humidities. This versatile cartridge would provide substantially improved protection for industrial workers potentially exposed to toxic gases, the composition of which is not necessarily known. The adsorbent would be useful in industrial respirators, military gas masks, and industrial adsorbents.

Objectives

In this work, a fraction of the pores in the activated carbon was filled with a low volatility, non-toxic, polar, organic liquid. The light, polar, organic vapor should dissolve in the heavy polar, organic liquid contained in these pores. The presence of the added organic liquid will not prevent the non-polar or weakly polar organics in the air stream from adsorbing on the surface of the untreated carbon pores. If the heavy organic was not toxic and had a high odor threshold, the very small amount that would escape into the air stream would not harm or annoy the respirator user. The

heavy organic liquid used to dope the activated carbon also could reduce the tendency of water to capillary condense in the adsorbent pores. The overall aim of this project is the development of a sorbent to solve either the problem of inefficient removal of toxic, volatile, polar organics or of decreased efficiency at high humidities.

Methodology

The heavy organic dopant was dissolved in methanol and added to the carbon. The mixture was allowed to equilibrate at a slightly elevated temperature, after which the methanol was removed by evacuating the sample. The equilibrium adsorption of toxic organics on modified and unmodified activated carbon was measured as a function of toxin partial pressure and relative humidity using a gravimetric adsorption apparatus. Saturated salt solutions were used to maintain constant humidities. The organic toxins investigated were acetaldehyde, carbon tetrachloride, and 1,2-propylene oxide. The dopants investigated were glycerol, squalene, and 1-dodecanol.

Significant Findings

1. Modifying the activated carbon with the heavy organic dopants used in this investigation decreases the condensation of water vapor in the micropores of the carbon.
2. Modifying the activated carbon decreased the equilibrium adsorption of the low molecular weight, polar, organic compounds used in this investigation.

Human Metabolism of Halothane - Mechanisms of Toxicity

James R. Trudell, Ph.D.
Stanford University Medical Center
School of Medicine
Department of Anesthesia
Stanford, California 94305-5117

Program Area: *Other Occupational Needs*
Grant Number: *3 R01 OH00978-09S1*
Start & End Dates: *09/01/80 - 11/30/90*
Funding Level: *$292,338 ($1,859,515 Cum)*

Importance to Occupational Safety and Health

The set of studies with halothane, isoflurane, carbon tetrachloride, dibromoethane, and styrene validate our *in vitro* test system for examining the effects of hepatotoxins. Both dibromoethane and styrene have been targeted by NIOSH because of their occupational exposure. In that we are able to prepare approximately 200 hepatocyte monolayers from a single rat, we have accomplished a national goal of reducing the number of animals sacrificed in research. Our study with the new anti-tumor drug SR 4233 shows that with this *in vitro* assay system, it is possible to propose probable hepatotoxicity based on its chemical structure, and then test for this toxicity in hepatocyte monolayers.

Our studies with neutrophil-mediated cytotoxicity lend support to a mechanism of hepatotoxicity that may have general applicability to many toxic chemicals. Following an acute exposure to a chemical, reactive metabolites are produced that bind to proteins in the liver, and these modified proteins elicit the production of specific antibodies. If a second acute or chronic exposure to the chemical occurs, these circulating antibodies will bind to the surface of hepatocytes that have metabolized the chemical. Then macrophages, attracted by products of lipid peroxidation and activated by immune complexes, will attack the cells that have bound antibodies and attempt to lyse them. Chronic second exposures that are of too low a level to induce lysis will result in persistent attack by activated macrophages. There is evidence that such a persistent inflammation may initiate carcinogenesis. This hypothesis would suggest that persons who incur an initial high acute exposure to a toxic chemical should be tested for circulating antibodies against metabolites of this chemical, and, if present, be warned against re-exposure.

Objectives

We are studying three interrelated aspects of the hepatotoxicity of halothane and related halogenated hydrocarbons: First, the mechanism by which metabolism of halothane or dibromoethane causes acute hepatic necrosis by rapid damage to essential cellular proteins; second, the metabolic pathway by which formation of free radical metabolites of these halogenated hydrocarbons leads to peroxidation of cell membrane phospholipids and how some of these peroxidized phospholipids may be converted into potent mediators of inflammation and activators of macrophages; and third, the induction of antibodies in certain individuals against metabolites of halogenated hydrocarbons to which they have been exposed and the mechanism by which a second acute exposure or continued chronic exposure may cause circulating macrophages to attack liver cells. Of particular importance is how these chronically activated macrophages may initiate carcinogenesis.

Methodology

Rat liver cells were isolated and maintained in monolayer culture for our studies of the acute toxicity of halothane and other agents. These monolayer cell cultures were used as targets for the studies of neutrophil-mediated cytotoxicity. Human neutrophils were isolated from human donor blood, the neutrophils were activated with PMA, and lysis of the hepatocytes was measured.

In a series of studies, the mechanism of production of leukotriene B_4 (LTB_4) in liver cells was studied by isolating LTB_4 with high pressure liquid chromatography (HPLC), confirming its structure with desorption chemical ionization mass spectrometry (DCI-MS), and measuring its activity with RIA.

We have raised antibodies (anti-TFA-RSA IgG) in rabbits against a trifluoroacetylated albumin adduct (TFA-RSA). We have prepared synthetic N-trifluoroacetyl-phosphatidylethanolamine (N-TFA-PE) adducts. We have used flow cytometry to measure binding of anti-TFA-RSA-IgG antibodies to micelles containing N-TFA-PE adducts.

Significant Findings

The individual contribution of halothane metabolism, hepatic enzyme induction, and hypoxia to hepatotoxicity were measured *in vitro* in our hepatocyte monolayer assay system. This study showed that halothane metabolism is an essential factor and that hepatotoxicity is not due to

decreased hepatic oxygenation, as has been suggested by others. In this same study, it was shown that hypoxia and enzyme induction exacerbate the toxicity of halothane, but another inhalation anesthetic (isoflurane) that was used as a control was not toxic. In separate studies, the same *in vitro* assay system was used to measure the effect of hypoxia on the toxicity of carbon tetrachloride, dibromoethane, styrene, and a new anti-tumor agent, SR 4233.

We have previously shown that during metabolism of halothane, hepatocytes produce 5-hydroperoxyeicosatetraenoic acid (5-HPETE), a product of lipid peroxidation. We have developed two sensitive assays for 5-HPETE and leukotrienes. We have now shown that hepatocytes are capable of converting 5-HPETE into leukotriene B_4. This demonstrates that damaged hepatocytes could release powerful chemoattractants, such as leukotriene B_4, that would attract circulating macrophages. This newly discovered ability supports the immune mechanism of hepatotoxicity that is discussed above.

We have shown that stimulated neutrophils are able to overcome the metabolic defenses of hepatocytes and lyse them. Proof of this ability of neutrophils to lyse hepatocytes was essential to our proposal that antibody-mediated attack may be involved in some forms of hepatotoxicity initiated by environmental chemicals.

We have shown that anti-TFA-RSA IgG antibodies bind to N-TFA-PE in phospholipid micelles. The demonstration of cross-reactivity of antibodies raised against a protein antigen with haptenic groups on a phospholipid may be of importance in understanding delayed onset halothane hepatotoxicity. In addition, this mechanism may contribute to immune-mediated cytotoxicity due to a number of other environmental toxins.

Publications

Trudell JR, Ardies CM, Anderson WR: Cross-reactivity of Antibodies Raised Against Acetaldehyde Adducts of Protein with Acetaldehyde Adducts of Phosphatidylethanolamine: Possible Role in Alcoholic Cirrhosis. Mol Pharmacol, in press, 1990

Trudell JR, Ardies CM, Green CE, Allen K: Binding of Anti-acetaldehyde IgG Antibodies to Hepatocytes with an Acetaldehyde-phosphatidylethanolamine Adduct on their Surface. Alcoholism, in press, 1990

Trudell JR, Ardies CM, Anderson WR: Antibodies Raised Against Trifluoroactylated Protein Bind to Trifluoroacetyl Adducts of Phosphatidyl-ethanolamine: A Possible Component of Immune-Mediated Halothane Hepatitis. J Pharmacol Exp Ther, in press, 1990

Trudell JR, Ardies CM, Anderson WR: The Effects of Alcohol and Anesthetic Metabolites on Cell Membranes: A Possible Direct Immune Mechanism. In: Molecular and Cellular Mechanisms of Alcohol and Anesthetics, (eds. S Roth, KW Miller), Ann NY Acad Sci, in press, 1990

Costa AK, Trudell JR: Toxicity of Styrene Vapor in Hepatocyte Monolayers at Low Oxygen Tensions. Environ Health Perspect 84:209-213, 1990

Heffel DF, Costa AK, Schieble TM, Trudell JR: Neutrophil-mediated Cytotoxicity in Confluent Monolayers of Rat Hepatocytes. Biochem Arch 5:229-235, 1989

Trudell JR, Gut J: Properties of Enzymes in Hepatocytes that Convert 5-HPETE or LTA_4 into LTB_4. Free Rad Biol Med 7:275-284, 1989

Costa AK, Baker MA, Brown JM, Trudell JR: Hepatotoxicity of SR 4233, 3-amino-1,2,4-benzo-triazine-1,4-dioxide, a Hypoxic Cytotoxin and Potential Anti-Tumor Agent. Cancer Res 49:925-929, 1989

Costa AK, Trudell JR: Interaction of Hypoxia and Carbon Tetrachloride Toxicity in Hepatocyte Monolayers. Exp Mol Pathol 50:183-192, 1989

Schieble TM, Costa AK, Heffel DF, Trudell JR: Comparative Toxicity of Halothane or Isoflurane Exposure, Hypoxia, and Phenobarbital Induction in Monolayer Cultures of Rat Hepatocytes. Anesthesiology 68:485-494, 1988

Gut J, Jamieson GC, Trudell JR: Leukotriene Biosynthesis: Direct Chemical Ionization Mass Spectrometry of Underivatized Arachidonic Acid Metabolites. Biomed Environ Mass Spectrom 15:509-516, 1988

Costa AK, Trudell JR: Toxicity of 1,2-Dibromoethane in Primary Hepatocyte Monolayer Cultures: Lack of Dependance on Oxygen Concentration. Toxicol Appl Pharmacol 95:241-247, 1988

Gut J, Goldman DW, Trudell JR: Conversion of 5-Hydroperoxyeicosatetraenoic Acid (5-HPETE)

into Leukotriene B_4 by Rat Hepatocytes: A Novel Cellular Source for Leukotriene B_4. Mol Pharmacol 34:256-264, 1988

Gut J, Jamieson GC, Trudell JR: Direct Chemical Ionization Mass Spectrometry of Underivatized Arachidonic Acid Metabolites: Application to Leukotriene Biosynthesis. In: Oxygen Radicals in Biology and Medicine, (ed. C Simic), Plenum Press, New York, pp 185-189, 1988

Gut J, Jamieson GC, Trudell JR: Quantification of 5- and 15-HPETE's by Direct Chemical Ionization Mass Spectrometry. Free Rad Biol Med 3:323-328, 1987

Gut J, Goldman DW, Jamieson GC, Trudell JR: Conversion of Leukotriene A_4 to Leukotriene B_4: Catalysis by Human Liver Microsomes under Anaerobic Conditions. Arch Biochem Biophys 259, 497-509, 1987

Costa AK, Heffel DF, Schieble TM, Trudell JR: Toxicity of T-butyl Hydroperoxide in Hepatocytes Exposed to Hypoxia and Reoxygenation. In Vitro 23:501-506, 1987

Trudell JR: Ethyl Acetate Extraction of Spin-trapped Free Radicals: A Re-evaluation. Free Rad Biol Med 3:133-136, 1987

Shapiro JM, Mihm FG, Trudell JR, Stevens JH, Feeley TW: Leukotriene D_4 Increases Extravascular Lung Water in the Dog. Circ Shock 21:121-128, 1987

Costa AK, Schieble TM, Heffel DF, Trudell JR: Toxicity of Calcium Ionophore A23187 in Monolayers of Hypoxic Hepatocytes. Toxicol Appl Pharmacol 87:43-47, 1987

Trudell JR, Gut J, Costa AK: Leukotrienes in Hepatocyte Injury. In: Modulation of Liver Cell Expression, (eds. D Keppler, H Popper), MTP Press, Lancaster, England, pp 411-421, 1987

Gut J, Costa AK, Trudell JR: Interaction of Cytochrome P450 with NADPH Cytochrome P450 Reductase and Cytochrome b_5. In: Membrane Proteins, (ed. S Goheen), Biorad Publications, Richmond, CA, pp 31-44, 1987

Gut J, Costa AK, Trudell JR: Oxygen Concentration-dependent Metabolism of Leukotriene A_4 by Hepatocyte Monolayers. Biochim Biophys Acta 878:194-199, 1986

Trudell JR: Metabolism of Nitrous Oxide. In: Nitrous Oxide/N20, (ed. EI Eger, II), Elsevier, New York, pp 203-210, 1985

Trudell JR, Bendix M, Bösterling B: Hypoxia Potentiates the Toxicity of Leukotrienes, Hydroperoxyeicosatetraenoic Acids, or Calcium Ionophore A23187 in a Hepatocyte Monolayer *In Vitro* Test System. In: *In Vitro* Toxicology, (ed. AM Goldberg), Liebert, New York, pp 695-708, 1985

Trudell JR, Bendix M, Bösterling B: Hypoxia Potentiates Killing of Hepatocyte Monolayers by Leukotrienes, Hydroperoxyeicosatetraenoic Acids, or Calcium Ionophore A23187. Biochim Biophys Acta 803:338-341, 1984

Bösterling B, Trudell JR: 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: Use of Spin Labels in the Study of Drug Effects on Membranes. In: Spin Labeling in Pharmacology, (ed. JL Holtzman), Academic Press, Inc., Orlando, Florida, pp 159-173, 1984

Bösterling B, Trudell JR: Evidence for Leukotriene A_4 as an Intermediate in the Conversion of 5-HPETE to Leukotriene B_4 Catalyzed by Cytochrome P-450. Biochem Biophys Res Commun 115:995-1001, 1983

Bösterling B, Trudell JR: Leukotriene A_4 Metabolism by Hepatic Cytochrome P-450. Biochem Biophys Res Comm 114:850-854, 1983

Trudell JR, Bösterling: Interactions of Cytochrome P-450 with Phospholipids and Proteins. In: Membrane Fluidity in Biology: Concepts of Membrane Structure, (ed. R Aloia), Academic Press, New York, pp 201-233, 1983

Bösterling B, Trudell JR, Trevor AJ, Bendix M: Lipid-protein Interactions as Determinants of Activation or Inhibition by Cytochrome b_5 of Cytochrome P-450 Mediated Oxidations. J Biol Chem 257:4375-4380, 1982

Trudell JR, Bösterling B, Trevor AJ: Reductive Metabolism of Halothane by Human and Rabbit Cytochrome P-450: Binding of 1-chloro-2,2,2-trifluoroethyl Radical to Phospholipids. Mol Pharmacol 21:710-717, 1982

Bösterling B, Trevor AJ, Trudell JR: Binding of Halothane Free Radicals to Fatty Acids Following UV Irradiation. Anesthesiology 56:380-384, 1982

Bösterling B, Trudell JR: Association of Cytochrome b_5 and Cytochrome P-450 Reductase with Cytochrome P-450 in the Membrane of Reconstituted Vesicles. J Biol Chem 257:4783-4787, 1982

Trudell JR, Bösterling B, Trevor AJ: Reductive Metabolism of CCl_4 by Human Cytochromes P-450 Reconstituted in Phospholipid Vesicles: Mass Spectral Identification of Trichloromethyl Radical Bound to Dioleoylphosphatidylcholine. Proc Natl Acad Sci USA 79, 2678-2682, 1982

Bösterling B, Trudell JR: Phospholipid Transfer between Vesicles: Dependence on Presence of Cytochrome P-450 and Phosphatidyl Choline-phosphatidylethanolamine Ratio. Biochim Biophys Acta 689:155-160, 1982

Bösterling B, Trudell JR, Trevor A: Use of Vesicles of Reconstituted Human Cytochrome P-450 in Studies if Free Radical Production by Reductive Metabolism of Halocarbons. In: Cytochrome P-450, Biochemistry, Biophysics, and Environmental Implications, (eds. E Hietanen, M Laitinen, O Hanninen), Elsevier Biomedical Press, Amsterdam, pp 619-622, 1982

Bösterling B, Trudell JR: Lipid-protein Interactions as Determinants of the Association of Cytochrome b_5 and Cytochrome P-450 Reductase with Cytochrome P-450. In: Cytochrome P-450, Biochemistry, Biophysics and Environmental Implications, (eds. E Hietanen, M Laitinen, O Hanninen), Elsevier Biomedical Press, Amsterdam, pp 497-500, 1982

Trudell JR, Bösterling B, Trevor A: 1-Chloro-2,2,2-trifluoroethyl Radical: Formation from Halothane by Human Cytochrome P-450 in Reconstituted Vesicles and Binding to Phospholipids. Biochem Biophys Res Comm 102:372-377, 1981

Bösterling B, Galla HJ, Trudell JR: Phospholipid Interactions with Cytochrome P-450 in Reconstituted Vesicles: Preference for Negatively-charged Phosphatidic Acid. Biochem Biophys Acta 643:547-556, 1981

Edmunds HN, Trudell JR, Cohen EN: Low Level Binding of Halothane Metabolites to Rat Liver Histones *In Vivo*. Anesthesiology 54:298-304, 1981

Bösterling B, Trudell JR: Spin Trap Evidence for Production of Superoxide Radical Anions by Purified NADPH-cytochrome P-450 Reductase. Biochem Biophys Res Comm 98:569-575, 1981

Bösterling B, Trudell JR: Formation of Free Radical Intermediates during Nitrous Oxide Metabolism by Human Intestinal Contents. Biochem Pharmacol 29:3037-3038, 1980

Bösterling B, Trudell JR: Purification of Human and Rat Cytochromes P-450 and P-450 Reductase and their Reconstitution into Phospholipid Vesicles. In: Microsomes, Drug Oxidations, and Chemical Carcinogenesis, (ed. MJ Coon), Academic Press, New York, pp 115-118, 1980

Chromium Distribution and Toxicity in Mammalian Cells

Edwin M. Uyeki, Ph.D.
The University of Kansas Medical Center
39th Street and Rainbow Boulevard
Kansas City, Kansas 66103

Program Area: *Other Occupational Needs*
Grant Number: *5 R01 OH01630-07*
Start & End Dates: *09/30/83 - 08/31/91*
Funding Level: *$150,104 ($713,490 Cum)*

Importance to Occupational Safety and Health

Light microscopic analyses are among those most sensitive in detecting injury to cells. By using computer-aided microscopy (CAM), quantitation of the early injury to cells is possible. These studies provide an early assessment and quantitation of injury to cells by occupational toxicants such as chromate [Cr(VI)].

Objectives

We are conducting a computer-aided microscopy (CAM) study of acute and chronic hepatotoxicity of sodium dichromate injected into mice. Within 6 hours of an ip injection of chromate (25 mg/kg), apoptotic bodies were observed at the epithelial surface of the liver; this is the first such report of apoptosis as a feature of chromate toxicity. We are therefore comparing the multi-phasic response of the liver to an apoptogen (chromate) and to a necrogen (carbon tetrachloride). Each

toxicant generated a unique pattern of response, viz., cell injury/death, inflammation, and repair of the liver. Of the 3 phases, we will experimentally ask: What is the nature of the injury, when does it occur, and where is the location of the injury?

Methodology

Of the techniques used to detect injury in tissues, light-microscopic analyses are among those most sensitive in detecting injury to cells. This sensitivity arises from the ability of such techniques to visually select the "one-cell-among-many" (OCAM) which are "different" from surrounding cells. The major advantages of this technique are that one can identify which cells (OCAM) are affected, describe their characteristic staining pattern, and the regional area of the injury. Currently, batch-processing (biochemical) techniques are used as the putative methodology for toxicology as well as all quantitative biomedical sciences. While these techniques have been valuable in the quantitative evaluation of toxicants, they do not address the methodological problems associated with the analysis of one-cell-among-many: The use of batch-processing techniques, by homogenization or cell dispersal obscures the contribution of different cell types to the measured event/content, as well as the loci of injury.

The main drawback to microscopic or pathologic analyses is that, for the most part, they are descriptive and lack quantitation needed for statistical analyses. The advent of new technologies for the capture, digitization, and storage of light-microscopic images, obtained through the union of the light-microscope with television and computers, has given rise to a new methodology with quantitative rigor.

Significant Findings

Several significant features of sodium dichromate hepatotoxicity, *in vivo*, were observed in mice treated with a sublethal dose (25 mg/kg). Specifically, a regional (focal) response to chromate injection, viz., apoptosis, was observed in periportal regions but not in pericentral regions. Because these apoptotic cells first occur at the epithelial surface of the liver 6 hours post-injection, but not in controls, we suggest these apoptotic cells are early signs of contact injury. Chromate appears to cause regional toxicity, primarily affecting cells in the periportal region.

Ploidy of the liver parenchyma appears to be influenced by several factors; animal age is a major factor. Chromate appears to accelerate the normal process of polyploidization in the mouse liver. This increase in ploidy state occurred in all regions of the liver and was not confined to the periportal region.

We examined the effects of chromate treatment on the PAS staining, as an indication of glycogen content of hepatocytes. Our studies showed that PAS staining was significantly decreased in the livers of mice, 6 hr and 2 days after injection, but not at 1 and 3 days after injection.

We developed an efficient and objective methodology for determining ploidy from histological material. Invariably, there are drawbacks to any procedure for determining ploidy. When working with histological material, many nuclei are incomplete, having been cut during the sectioning procedure. If all nuclei are measured, regardless of sectioning, the resulting distribution of nuclei are poorly differentiated. Discarding incomplete nuclei from measurement tends to disproportionately reduce the percentage of large nuclei which are counted. Measuring relatively thick histological sections minimizes the percentage of unmeasured large nuclei, but increases the percentage of nuclei which cannot be measured because of overlap. This overlap phenomenon leads to an underestimate of the percentage of small nuclei, since (1) unlike octaploid cells, a large percentage of the diploid cells in the mouse liver are binucleate with the nuclei in close proximity to one another and (2) diploid cells are smaller than tetraploid and octaploid cells and thus more closely packed. We found that 12 micron-thick sections provide the best compromise thickness for dealing with sectioning and overlap problems.

Publications

Garrison JC, Bisel TU, Uyeki EM: The Influence of Chromium Toxicity on Hepatocyte Ploidy as Analyzed By Microcomputer Imaging. Fundam Appl Toxicol 14:346-355, 1990

Garrison JC, Peterson P, Uyeki EM: Computer Analysis of Cartilage Differentiation in Embryonic Limb Bud Micromass Culture as Influenced by Dimethyl Sulfoxide, Sodium Butyrate and Benzamide. J Microscopy 156:353-361, 1989

Garrison JC, Uyeki EM: The Effects of Gamma Radiation on Chondrogenic Development *In Vitro*. Rad Res 116:356-363, 1988

Garrison JC, Petit G, Uyeki EM: Effect Phorbol and Bryostatin I on Chondrogenic Expression of Chick Limb Bud, *In Vitro*. Life Sciences 41:2055-61, 1987

Uyeki EM, Nakanishi S, Fremming L: Chromium Effects on Chrondrocytic Differentiation *In Vitro*. J Tox Environ Health 19:137-45, 1986

Poison Centers: A Resource for Occupational Health Services

C. Scott Clark, Ph.D., P.E., CIH
University of Cincinnati
College of Medicine
Department of Environmental Health
Cincinnati, Ohio 45267-0056

Program Area: *Other Occupational Needs*
Grant Number: *5 R18 OH01981-02*
Start & End Dates: *02/01/87 - 01/31/90*
Funding Level: *$165,593 ($321,937 Cum)*

Importance to Occupational Safety and Health

Regional poison centers are frequently called upon to provide information regarding potential or actual occupational exposures, but often do not have the training or resources to efficiently respond to these requests. The training needs assessment conducted as part of this project is the first national survey of existing training and training needs of poison center staff for occupational health services. The response protocols developed will be of potential use to poison control centers in efficiently and effectively responding to requests for occupational health information.

Objectives

This project is designed to determine the usefulness of regional poison control centers as both a disseminator of occupational health information and as an occupational disease surveillance mechanism after suitable training and the development of appropriate response protocols.

Methodology

The following activities are included in this project:

1. The development of an occupational health training course for poison information specialists of a regional poison center and evaluation of its use by the Cincinnati Drug and Poison Information Center staff (DPIC).
2. The development of model protocols for use by poison center occupational health specialists in responding to requests for information about specific dangerous chemical substances in the workplace. An evaluation of existing information sources, both printed and computerized, will identify the useful toxic substances management and prevention protocols to be used in the development of a uniform information and response system for poison center staff.
3. Occupational health professionals will assist the poison center to maximize the impact of these activities on the dissemination of quality information to the public.
4. The design of occupational health data sheets for use by the poison center for the collection of uniform data on each request and the quality of service provided by the poison center staff are evaluated by an industrial hygienist and occupational physician.
5. An evaluation of these data for their value as a surveillance method for the detection of occupational disease.

Significant Findings

In an evaluation of telephone responses to 185 occupational health inquiries received after poison staff had undergone training, almost two-thirds were handled using information sources: the Poisindex System, Chemical Hazards in the Workplace, and Occupational Health Guidelines for Chemical Hazards. In 70% of these cases, help from an environmental toxicologist or occupational medicine resident was also utilized in the response. Almost one-half of the inquiries were handled within 15 minutes each. In a comparison of inquires to DPIC with those of the local health department over the same time period, the proportion of calls from health professionals was three times higher for DPIC inquires. In an evaluation of 250 occupational/environmental calls, solvents were the most frequently cited exposure (30%), and most callers were not aware of the health risks involved.

Publications

Sublet VH, Sigell LT, Clark CS, Bonfiglio JF: Resources Utilized by Poison Specialists to Answer Occupational Environmental Requests. Veterinary and Human Toxicology 31(4):367, 1989 (Abstract)

Sublet VH, Clark CS, Sigell LT: An Occupational Environmental Disease Surveillance Program: Based in a Regional Poison Center. Veterinary and

Human Toxicology 31(4):346, August, 1989 (Abstract)

Bonfiglio JF, Clark CS, Sigell LT, Sublet VH, Rice CH, Radike MJ, Hayes KM: Poison Centers: A Resource for Occupational Health Services. Veterinary and Human Toxicology 30(6):569-571, 1988

Sublet VH, Linz D, Bonfiglio JF, Sigell LT, Clark CS, Kline S, Radike MJ: Occupational Environmental Protocols Designed for Use by Poison Information Specialists. Veterinary and Human Toxicology 30(5):455-458, 1988

Sigell LT, Hayes KM, Bonfiglio JF, Clark CS, Sublet VS, Millman S, Rice CH, Siegel EG: An Occupational/Environmental Service Training Program for Poison Information Specialists. Veterinary and Human Toxicology 31(4):367, August, 1988 (Abstract)

Bonfiglio JF, Clark CS, Sigell LT, Rice CH, Radike MJ, Hayes KM, Sublet VH: Poison Centers: A Resource for Occupational Health Services. Veterinary and Human Toxicology 2(6):467, December, 1987 (Abstract)

Hayes KM, Bonfiglio JF, Sigell LT, Clark CS, Millman S, Rice CH and Siegel EG: An Occupational/Environmental Service Training Program for Poison Information Specialists. Veterinary and Human Toxicology 2(6):487, December, 1987 (Abstract)

Sublet VH, Linz D, Bonfiglio JF, Sigell LT, Clark CS, Kline S, Radike MJ: Occupational/Environmental Protocols Designed for Use by Poison Information Specialists. Veterinary and Human Toxicology 2(6):488, December, 1987 (Abstract)

Effects of 27 MHz Radiation on Somatic and Germ Cells

Stephen F. Cleary, Ph.D.
Virginia Commonwealth University
Medical College of Virginia
Department of Physiology, Box 551
Richmond, Virginia 23298-0551

Program Area: *Other Occupational Needs*
Grant Number: *2 R01 OH02148-06*
Start & End Dates: *09/27/85 - 09/29/92*
Funding Level: *$141,934 ($764,770 Cum)*

Importance to Occupational Safety and Health

It is well documented that workers are routinely exposed to 27-MHz and other frequencies of electromagnetic radiation. Health protection guidelines are based upon the premise that adverse health effects are due to tissue heating. It is of primary importance for occupational safety and health to determine the validity of this premise. To this end, studies are being conducted of the effects of continuous wave (CW) and pulse-modulated (PM) 27-MHz and 2450-MHz RF electromagnetic radiation on mammalian cells *in vitro*.

Studies conducted to date provide firm evidence that these RF radiation frequencies affect cell mitotic activity under conditions that simulate occupational exposure. Whereas the mechanism is not well understood, it has been determined that it is a direct RF effect, not due to heating. These results indicate the need for detailed characterization of cellular effects of RF radiation to provide insight regarding: (a) the adequacy of the basis for present occupational exposure guidelines, and (b) mechanisms of direct RF-induced cellular alterations.

Objectives

The principal objective is to determine dose thresholds and dose-response relationships for effects of continuous wave (CW) and pulse-modulated (PM) 27-MHz and 2450-MHz RF radiation on mammalian cell proliferation *in vitro*. By comparing effects of 27-MHz RF with effects of exposure to 2450-MHz, the role of RF frequency is being investigated. Precise control of exposure conditions, such as temperature, will permit testing hypotheses regarding the mechanisms of

RF-induced alteration of mammalian somatic and germ cells.

Methodology

Cell suspensions are exposed to 27-MHz or 2450-MHz radiation under isothermal conditions *in vitro*. Viability and morphology are assayed immediately after exposure. Cells are cultured for 1, 3, or 5 days and functional assays (i.e., cell proliferation, mitogenesis, DNA, RNA, protein synthesis, sperm viability, and motility, *in vitro* fertilization) are conducted. Cytofluorimetry and dielectric spectroscopy are used to investigate the interaction of RF radiation with the cell cycle using synchronized populations of Chinese hamster ovary (CHO) and HeLa cells.

Significant Findings

A single 2 h isothermal (37 ± 0.2°C) exposure to either 27- or 2450-MHz RF radiation induces biphasic dose-dependent alterations in human lymphocyte mitogenesis 3d after exposure, or in DNA and RNA synthesis in glioma (LN71) cells 1, 3, or 5d after exposure. The threshold for RF effects on lymphocytes and glioma is being investigated. Exposure of either cell type to SARs in the range 5-50 W/kg stimulated biosynthetic processes, whereas exposure at > 50 W/kg suppressed cellular activity. Comparisons of the effects of CW versus PM (duty cycle 0.377) 27-MHz RF radiation indicate similar biphasic effects on human lymphocyte activation and glioma proliferation. RF exposure of lymphocytes or glioma *in vitro* at elevated temperature (39°C) altered proliferation relative to exposure at 37°C. This finding is potentially significant since *in vivo* RF exposures in the workplace are known to involve radiation-induced heating in some instances.

Dose-dependent RF-induced shifts in the cycle of synchronized CHO and HeLa cells indicate that the biphasic response results from cycle-specific effects on DNA/RNA synthesis. Maximum sensitivity for RF-induced cycle phase shifts appear to occur during Go/G_1 phase. A highly statistically significant reduction in the ability of mouse spermatozoa to fertilize mouse ova occurred following a 1 h exposure of sperm at 37 ± 0.2°C. RF exposure at SARs in the range of 5- to 200W/kg had no detectable effect on cell viability or morphology.

Publications

Cleary SF, Liu LM, Merchant RE: Lymphocyte Proliferation Modulated *In Vitro* by Isothermal Radiofrequency Radiation Exposure. Bioelectromagnetics 11:47-56, 1990

Cleary SF, Liu LM, Merchant RE: Glioma Proliferation Modulated *In Vitro* by Isothermal Radiofrequency Radiation Exposure. Radiation Research 121:38-45, 1990

Cleary SF: Biological Effects of Radiofrequency Electromagnetic Radiation. In: Biological Effects and Medical Applications of Electromagnetic Fields, Chapter 10, (ed. O Gandhi), Prentice Hall, Englewood Cliffs, New Jersey, 1990

Cleary SF: Cellular Effects of Radiofrequency Electromagnetic Radiation. In: Biological Effects and Medical Applications of Electromagnetic Fields, Chapter 14, (ed. O Gandhi), Prentice Hall, Englewood Cliffs, New Jersey, 1990

Cleary SF, Liu LM, Cao G: Functional Alteration of Mammalian Cells by Direct High Frequency Electromagnetic Field Interactions. In: Charge and Field Effects in Biosystems. Vol 2, Plenum Press, New York, pp 211-221, 1990

Cleary SF, Liu LM, Graham R, East J: *In Vitro* Fertilization of Mouse Ova by Spermatozoa Exposed Isothermally to Radiofrequency Radiation. Bioelectromagnetics 10:361-370, 1989

Cleary SF: Biological Effects of Non-ionizing Electromagnetic Radiation: An Overview. In: Electromagnetic Biointeraction: Mechanisms, Safety Standards, Protection Guides, (eds. G Franceschetti, OP Gandhi, M Grandolfo), Plenum Press, New York, pp 59-79, 1989

Liu LM, Cleary SF: Effects of 2.45 GHz Microwave and 100 MHz Radiofrequency Radiation on Liposome Permeability at the Phase Transition Temperature Bioelectromagnetics 9:249-257, 1988

Cleary SF: Biological Effects of Non-ionizing Electromagnetic Radiation. In: Encyclopedia of Medical Devices and Instrumentation, (ed. JG Webster), J Wiley & Sons, New York, pp 274-303, 1988

Plasma Proteins: Markers of Chemical Exposure

Ghulam A.S. Ansari, Ph.D.
University of Texas Medical Branch
Department of Human Biological Chemistry and Genetics
Galveston, Texas 77550-2774

Program Area: *Other Occupational Needs*
Grant Number: *5 R01 OH02149-05*
Start & End Dates: *01/01/89 – 08/31/92*
Funding Level: *$143,568 ($560,375 Cum)*

Importance to Occupational Safety and Health

The purpose of this study is to develop biological markers of chemical exposure. The chemical and biological assays thus developed to measure changes in plasma proteins can be used to monitor occupationally-exposed populations. Correlation between the changes in plasma proteins and the medical histories of the occupationally-exposed individuals can be used for medical surveillance as well as for risk assessment.

Objectives

A significant number of people are exposed to a variety of chemicals at work sites which may be responsible for toxic manifestations. Such exposure(s) can bring about changes in plasma proteins in terms of their function, concentration, or covalent modification. These changes, besides being responsible for toxic effects, can also be used as markers of chemical exposure. The intent of this research is to develop method(s) which can identify the changes in plasma proteins caused by chemical exposure.

Methodology

Effects of chemical exposure on plasma proteins were studied in terms of their biological activity, concentration, and covalent modification. These changes were measured by using bio- and immunoassays and electrophoretic and chromatographic techniques. Covalent modification was further characterized by peptide mapping and compositional and sequential amino acid analysis. The structure of the modified amino acid(s) was determined by spectral techniques.

Significant Findings

The loss of α-proteinase inhibitor (α_1-PI) activity in the lung has been proposed as a key factor in causing pulmonary emphysema. Earlier studies from this laboratory have shown that α_1-PI can be inhibited by aldehydes present in cigarette smoke and may contribute to the development of lung emphysema among cigarette smokers (Gan and Ansari, 1986). Acrolein was found to be the most potent inactivator which causes dose-dependent disappearance (modification) of lysine and histidine residues. Modification of 23 lysine and 8 histidine residues results in the loss of more that 90% of α_1-PI (Gan and Ansari, 1987). Four new peaks were observed upon amino acid analysis of α_1-PI which was inactivated by acrolein under *in vitro* conditions. The first peak emerged just before ammonia, the second and third, between ammonia and lysine, while the fourth was between histidine and arginine. The new fourth peak was also observed when model compounds of lysine (N-acetyllysine or polylysine) were reacted with acrolein and subsequently processed for amino acid analysis. This new compound was purified by high voltage paper electrophoresis and subjected to fast atom bombardment mass spectrometry which showed a protonated molecular ion at m/z 203 [M + H] followed by m/z 186 [M + H-NH_3]. This compound was thus identified as 3-oxopropyllysine, a lysine adduct of acrolein. Similarly, when a model polypeptide of histidine, polyhistidine, was reacted with acrolein under the same conditions as α_1-PI, three new peaks (besides histidine) emerged from the column. Their elution times corresponded to the first three new peaks found in the hydrolysates of acrolein treated α_1-PI.

Earlier, we explored the possibility of using glutathione S-transferase (GST) of red cells as a marker of chemical exposure (Ansari et al., 1987) and established the microheterogeneity in this enzyme using high-performance liquid chromatography (Singh et al., 1986). Now we have compared the red cell GST with other π class GST. Using peptide mapping techniques, we have shown that a minor difference does exist among enzymes of this class from different tissues (Ahmed et al., 1989).

In order to develop immunoassays for detection of covalently modified protein, we have incubated the human blood with [^{14}C]-ethylene oxide. The plateau of the covalent binding of ethylene oxide with blood proteins was reached at six hours. The blood thus obtained was separated into globin and albumin. Almost all the radioactivity found in blood proteins was associated either with albumin or globin. Binding to albumin was about three-fold

higher than globin. Iso-electric focusing (IEF), using a narrow range of pH, showed changes in the covalently modified proteins by the appearance of new bands with lower pI for modified albumin (4.45 for modified vs 4.6 for the unmodified albumin), and new bands with higher pI for the modified vs 7.38 for the unmodified globin. These changes were also detected using two-dimensional SDS-PAGE. Amino acid analysis showed modification of amino acid residues of albumin. Losses in the amino acid residues were consistent with the covalent modification by ethylene oxide.

Publications

Gan JC, Ansari GAS: Inactivation of Plasma α_1-proteinase Inhibitor by Acrolein: Adduct Formation with Lysine and Histidine Residues. Mol Toxicol, in press, 1990

Gan JC, Ansari GAS: Inactivation of Plasma α_1-proteinase Inhibitor by Aldehydes Found in Cigarette Smoke. SAAS Bull Biochem Biotech 3:32-36, 1990

Ahmad H, Medh RD, Singh SV, Caccuri AM, Ansari GAS, Awasthi YC: Comparative Studies with Glutathione S-transferase of Human Placenta, Lung, and Erythrocytes: Evidence of Structural Differences. Enzyme 42:129-135, 1989

Ahmad H, Medh RD, Singh SV, Caccuri AM, Ansari GAS, Awasthi YC: Anionic Glutathione S-transferases of Human Erythrocytes, Placenta and Lung: Evidence for Structural Differences. Enzyme 42:129-135, 1989

Sanduja R, Ansari GAS, Boor PJ: 3-Hydroxypropyl-mercapturic Acid: A Biological Marker for Exposure to Allylic and Related Compounds. J Appl Toxicol 9:235-238, 1989

Britt SG, Ansari GAS: Formation of Lipid Adducts by Carbon Tetrachloride. Clin Chem Enzyme Comms 1:305-311, 1989

Ahmad H, Singh SV, Medh RD, Ansari GAS, Kurosky A, Awasthi YC: Differential Expression of α, μ, and π Classes of Isozymes of Glutathione S-transferase in Bovine Lens, Cornea, and Retina. Arch Biochem Biophys 266:416-426, 1988

Ansari H, Gan JC, Barton BK: *In Vitro* Inactivation of Plasma α_1-proteinase Inhibitor by Epoxides and 1,2-dihaloethanes. Arch Environ Contam Toxicol 17:537-542, 1988

Ansari GAS, Gan JC, Barton BK: Synergistic Activation of Plasma α_1-proteinase Inhibitor by Aldehydes of Cigarette Smoke with Styrene Oxide and 1,2-dichloroethane. Arch Environ Contam Toxicol 17:533-536, 1988

Ansari GAS, Kaphalia BS, Boor PJ: Selective Pancreatic Toxicity of Palmitoylpentachlorophenol. Toxicol 46:57-63, 1987

Singh SV, Leal T, Ansari GAS, Awasthi YC: Purification and Characterization of Glutathione S-transferases of Human Kidney. Biochem J 246:179-186, 1987

Ansari GAS, Singh SV, Gan JC, Awasthi YC: Human Erythrocyte Glutathione S-transferase: A Possible Marker of Chemical Exposure. Toxicol Lett 37:57-62, 1987

Boor PJ, Sanduja R, Nelson TJ, Ansari GAS: *In Vivo* Metabolism of the Cardiovascular Toxin, Allylamine. Biochem Pharmacol 24:4347-4353, 1987

Gan JC, Ansari GAS: Plausible Mechanism of Inactivation of α_1-proteinase Inhibitor by Acrolein. Res Commun Chem Path Pharmacol 55:419-422, 1987

Kaphalia BS, Ansari GAS: 2-Chloroethylstearate: An *In Vivo* Fatty Acid Conjugate of 2-chloroethanol. Bull Environ Contam Toxicol 39:835-842, 1987

Upreti RK, Farooqui MYH, Ahmed AE, Ansari GAS: Toxicokinetics and Molecular Interaction of [^{14}C]-formaldehyde in Rats. Arch Environ Contam Toxicol 16:263-273, 1987

Farooqui MYH, Upreti RK, Ahmed AE, Ansari GAS: Influence of Intraperitoneally Administered Formaldehyde on Bile Production and Glutathione Levels in Rats. Res Commun Chem Path Pharmacol 53:233-236, 1986

Gan JC, Ansari GAS: Non-oxidative Inactivation of Plasma α_1-proteinase Inhibitor by Carbonyl Compounds Found in Cigarette Smoke. Res Commun Subs Abuse 7:59-69, 1986

Singh SV, Ansari GAS, Awasthi YC: Anion Exchange High Performance Liquid Chromatography of Glutathione S-transferases: Separation of the Minor Isozymes of Human Erythrocytes, Heart, and Lung. J Chromatogr 361:337-345, 1986

Dose/Response for Styrene Exposures

Stephen M. Rappaport, Ph.D.
University of North Carolina
School of Public Health
Department of Environmental Sciences and Engineering
CB #7400 - Campus
Chapel Hill, North Carolina 27599-7400

Program Area: *Other Occupational Needs*
Grant Number: *2 R01 OH02221-03A1*
Start & End Dates: *09/29/86 - 09/27/91*
Funding Level: *$211,904 ($470,488 Cum)*

Importance to Occupational Safety and Health

The project represents one of the first comprehensive applications of biochemical epidemiology to an occupational cohort. The extensive exposure assessment, performed longitudinally, minimized problems involving bias and the associated misclassification which are typically encountered. This study design has allowed us to detect elevated levels of SCEs at styrene concentrations below those which had heretofore been reported. The development and application of methods for detecting styrene-7,8-oxide (SO) adducts of DNA (SO-DNA) and hemoglobin (SO-Hb) will produce important new information concerning the bioavailability of SO in humans exposed to styrene.

Objectives

This study is investigating the linkages between exposure, uptake, and genotoxic response resulting from occupational exposure to styrene in the reinforced-plastics industry. A longitudinal assessment of exposure was completed in which 48 subjects were monitored in a single facility where fiberglass boats were manufactured. The primary purpose of the study is to accurately estimate the airborne exposure and uptake of each individual in the cohort for comparison with several indices of genotoxic response measured in blood samples, i.e., sister-chromatid exchanges (SCEs) in peripheral lymphocytes and the adducts, SO-Hb and SO-DNA. This would allow exposure-dose-response relationships to be established for styrene and for SO arising from metabolism of styrene *in vivo*. A secondary objective is to correlate the above indices of styrene uptake and genotoxicity with each other in a common pool of samples where exposure had been carefully documented.

A separate aspect of the investigation concerned the application of a pharmacokinetic model for styrene, derived under constant-exposure conditions, to the situation typical of occupational exposures where air levels vary greatly over time. The objective of this investigation was to determine the extent to which tissue concentrations of styrene in these compartments were damped compared to the air levels.

Methodology

Each individual's airborne exposure was measured 7 times (shift-long sampling), his/her blood was collected 4 times, and his/her exhaled air was collected up to 25 times over a 12-month period. Exposures were measured with passive monitors employing coconut carbon. Measurement of styrene in the exhaled air employed a new device which collects styrene from 3 liters of mixed exhaled air in a tube containing 200 mg of coconut carbon. Both types of samples were analyzed by solvent desorption/gas chromatography. Blood styrene was measured via the head space technique using standard addition and gas chromatography. SCEs were measured by the standard method. SO-DNA is to be measured by a modification of the ^{32}P-postlabeling technique. A new technique has been developed for measuring SO-Hb, which takes advantage of a metal catalyst (Raney nickel) to selectively cleave SO-cysteine adducts of Hb to yield 1- and 2-phenylethanol, which are subsequently derivitized and measured by gas chromatography with electron-capture detection. Concerning the numerical analysis, the input to the pharmacokinetic model was a lognormally-distributed, autocorrelated series of exposure concentrations while the output consisted of the resulting concentrations of styrene in the central and peripheral compartments.

Significant Findings

The exposure assessment was completed with analysis of styrene in all samples of air, exhaled air, and blood. Individual mean exposures ranged between 0.2 and 55 ppm for the 48 subjects with an overall mean of 15.1 ppm. There was a strong linear correlation between the styrene concentrations in exhaled air and blood (r^2 = 0.79, n = 109), indicating that the method of exhaled-air measurement is predictive of the uptake of styrene in the body. The relationship between the mean exhaled-air concentrations/subject and shift-long exposure/subject also showed a strong linear

correlation (r^2 = 0.76, n = 48); this indicates that differences in individual rates of uptake, which might arise from skin contact, respirator use, or differences in physiological parameters, were relatively minor.

SCEs have been scored from two of the four sets of blood samples. Preliminary results suggest that styrene exposure was significantly correlated with the number of SCEs/cell (r^2 = 0.211, p = 0.0001, n = 48). This indicates that styrene exposure below 50 ppm contributed to elevated SCEs; such findings of SCEs at these levels of styrene exposure have not been reported before.

We successfully applied the ^{32}P-postlabeling technique to *in vitro* modified samples of nucleosides, DNA, and cells and in selected samples of human DNA obtained from this study. The results clearly show that five SO-DNA adducts have been detected. Recent work by collaborators has confirmed the identities of these adducts in the *in vitro* modified samples as products of reaction of SO at N^2-, O^6-, N-7-, and C-8- positions of guanine.

The methods for measurement of SO-Hb has thus far achieved a sensitivity of 0.1 nmol of adduct per g of globin. When SO was reacted with whole human blood *in vitro* at SO concentrations between 0 and 318 nmol/ml a significant linear correlation (r^2 = 0.94) was obtained suggesting that the production of adducts was proportional to the concentration of SO over this range.

Results of numerical simulations employing the pharmacokinetic model suggest that the burdens of styrene in the central and peripheral compartments are likely to be highly damped compared to the air concentrations. The coefficients of variation of the series of burdens varied between about 30-50% of that associated with exposure (averaging time = 15 min) in the central compartment and between about 10-20% of CV in the peripheral compartment.

Publications

Rappaport SM, Spear RC: Physiological Dampening of Exposure Variability During Brief Periods. Ann Occup Hyg 32:21-33, 1988

Liu SF, Rappaport SM, Pongracz K, Bodell W: Detection of Styrene-Oxide DNA Adducts in Lymphocytes of a Worker Exposed to Styrene. In Methods for Detecting DNA-Damaging Agents in Humans, Appl in Cancer Epidemiology and Prevention (eds. H Bartsch, K Hemminki, IK O'Neill), IARC Sci, Publ #89, Lyon, pp 217-222, 1988

Lui SF, Rappaport SM, Rasmussen J, Bodell WJ: Detection of Styrene-Oxide-DNA Adducts by ^{32}P-Postlabeling. Carcinogenesis 9:1401-1404, 1988

Yager JW, Paradisn W, Symanski E, Rappaport SM: Sister-Chromatid Exchanges Induced in Peripheral Lymphocytes of Workers Exposed to Low Concentrations of Styrene. Proc of the Fifth International Conference on Environmental Mutagens, (ed. M Mendelsohn) 1989

Selvin S, Rappaport SM: A Note On The Estimation of The Mean From a Lognormal Distribution. Am Ind Hyg Assoc J in press, (1989)

Rappaport SM, Kure E, Petreas M: A Convenient Method For Measuring Solvent Vapors in Exhaled Air. The American Industrial Hygiene Conference, St. Louis, MO, May 1989

Artificial Intelligence Occupational History

Philip I. Harber, M.D., M.P.H.
University of California, Los Angeles
Occupational Medicine Branch
Department of Medicine, UCLA
Los Angeles, California 90024-1690

Program Area: *Other Occupational Needs*
Grant Number: *5 R01 OH02288-02*
Start & End Dates: *05/01/87 - 04/30/90*
Funding Level: *$141,724 ($248,018 Cum)*

Importance to Occupational Safety and Health

Occupational health expertise must be made generally available to optimally benefit workers. Unfortunately, although most clinicians have had minimal training in occupational health, they are the primary interface for detecting and treating occupational disease. Artificial intelligence (AI) methods not only provide such information, but can also incorporate logical processes to deal with incomplete and uncertain data.

Objectives

The project is aimed to develop a pilot AI system for utilization of knowledge of occupational lung disease. In addition, the methods are to be

generalizable for extension to other occupational health concerns.

Methodology

The Artificial Intelligence Occupational History System (AIOHS) is a complete artificial intelligence based expert system for the recognition of occupational lung disease. It includes several major components - the knowledge base, the inference engine, the user interface, and the development system.

A "knowledge structure" that includes all relevant facts was developed. It is relatively simple in structure, yet flexible in the types of information which can be incorporated. It consists of two types of records - those describing "objects" (terms) and those describing pairwise relations between terms. Appropriate modifiers are incorporated into the relations files. For example, a job-to-job relation is modified by the degree to which they actually are associated. For job-to-exposure relations, quantifiers include the frequency with which workers in the job category have the exposure and the typical level of exposure.

For the knowledge base, information from several textbooks and other sources was encoded according to pre-specified algorithms designed to minimize any biases.

An additional component of knowledge deals with uncertainty. Some "facts" are more certain (generally accepted) than others. A certainty factor (CF) has been assigned to each of the facts where such information is available in the primary source.

The inference engine operates upon the knowledge base (organized collection of facts), selecting those facts which are relevant to a particular case (data from a specific worker). The inference engine is independent of the knowledge base. The inference engine infers from job information the exposures and, subsequently, diseases which might be caused. These are then compared to those which the individual has, and then the possibilities are narrowed. Furthermore, additional information pertinent only to the specific case may be requested if it seems relevant.

The inference engine operates in a quantitative manner, using predicate calculus and taking into account the uncertainties of the individual facts along the causal path. It also considers the time course relative to the specific worker/patient.

The user interface provides the interaction between the computer and the user. A "user-friendly" system was implemented within the dBASE environment to include multiple windows, pull-downs, help statements, etc., in order to facilitate the interaction.

The user interface also includes an expert system itself. This system is used to make diagnoses of general disease categories based on symptoms, etc. The system is flexible in that it operates with varying amounts of information which the user may have, thereby differing from most algorithmic systems. It adjusts the likelihood of diagnoses based upon several factors, and it selectively requests additional clinical information only when relevant.

Significant Findings

1. Artificial Intelligence methods hold promise in occupational health, offering advantages over simple databases.
2. Appropriate information can be incorporated into fixed structures permitting computer implementation.
3. Development and testing require considerable effort.
4. This method can provide primary practitioners with levels of expertise rarely available, encouraging them to consider occupational factors in causing lung disease.
5. AI based exposure evaluation appears potentially useful in epidemiologic surveillance.

Publications

Harber P, McCoy JM, Shimozaki S, Coffman P, Bailey K: The Structure of Expert Diagnostic Information in Occupational Medicine. Am J Ind Med, in press, 1990

Harber P, Levin M, McCoy JM, Bailey K, Howard K, Brown C: Clinic Based Surveillance for Hazards: Questionnaire, Expert, and Expert System Approaches. Am Rev Respir Dis 141:A594, 1990 (Abstract)

Harber P, McCoy JM: Predicate Calculus, Artificial Intelligence, and Workers' Compensation. J Occup Med 31:484-89, 1989

Harber P, McCoy JM, Bailey K, Coffman P, Shimozaki S: Artificial Intelligence System for Recognition of Occupational Lung Disease. Am Rev Respir Dis 139:A552, 1989 (Abstract)

Hydrocarbon Exposure and Chronic Renal Disease

Nabih R. Asal, Ph.D.
University of Oklahoma at Oklahoma City
Health Sciences Center
801 NE 13th Street
Oklahoma City, Oklahoma 73190

Program Area: *Other Occupational Needs*
Grant Number: *5 R01 OH02391-02*
Start & End Dates: *09/15/89 - 09/14/92*
Funding Level: *$196,716 ($378,719 Cum)*

Importance to Occupational Safety and Health

Occupational exposure to nephrotoxins has for many years been suggested as an important etiological factor in chronic renal failure. However, only a few epidemiologic studies have attempted to clarify this suspicion. There is little doubt that chronic tubulointerstitial nephropathy may result from heavy metal toxicity; however, this is a relatively rare cause of chronic renal failure. In contrast, although hydrocarbons have been clearly implicated as a cause of chronic renal disease, there are reports suggesting that these ubiquitous agents may be associated with the development of a variety of chronic glomerulopathies.

There is patients an ever increasing number of end-stage renal disease (ESRD) (patients requiring dialysis or having had a renal transplant). They have become a major factor in Medicare expenditures. Elucidating the processes leading to ESRD and finding ways to control them are the most valid ways to reduce the personal, social, and economic hardships produced by this condition.

Objectives

The objective of this study is to investigate the role of chronic exposure to hydrocarbons in causing chronic renal disease.

Methodology

An ongoing population-based case-control study will be conducted utilizing patients and controls identified from two major counties in Oklahoma. Cases will include all adult patients between the ages of 18 and 79 with chronic renal disease (both those with ESRD and those not yet at that stage) having a confirmed diagnosis of idiopathic chronic glomerulopathy (ICG) as their primary disease and patients with chronic renal failure who have an unknown primary disease. Minimum criteria for diagnosis of ICG will include either a histologic diagnosis or the presence of unexplained proteinuria exceeding 2 gms/24 hrs. All new cases diagnosed between January 1, 1985 and July 31, 1992 meeting these criteria will be included in the study.

A general population-based control group matched to the cases by age (± 5 yrs.) and sex will be selected from the same communities by a Random Digit Dialing technique.

A detailed questionnaire will be administered to cases and controls. The questionnaire will include information on medical history, family history of chronic renal disease, medication history, smoking and beverage use, life-time occupational history specific for hydrocarbon exposure, demographics, and other pertinent data.

An exposure index to hydrocarbons will be calculated, using the expertise of several industrial hygienists, and used in a univariate and multivariate statistical analysis of risk factors for chronic renal disease. The univariate analysis will employ the odds ratio and multivariate analysis will employ Cox's Linear Logistic Regression Model.

The target number of total cases and controls will be 500 each. The study began on September 15, 1989 and will continue for three years.

Significant Findings

Preliminary findings are not yet available since all effort to date has been in the development of instruments and protocol for the Random Digit Dialing, hiring/training of personnel, logistics, arrangements with hospitals and nephrologists, abstracting of hospital records, and interviewing of cases and controls. Approximately 4,200 records have been viewed at the hospitals in the Oklahoma City area, and of these, 525 have been abstracted. Of the 525 abstracted records, 200 were determined to be valid cases, 200 were not cases, and 125 are possible cases pending further information. Of the 200 definite cases, 109 have been interviewed, 51 are in the process of being contacted, and 40 have been lost to interview because they refused, have died or could not be located. To date, 35 controls have been located and interviewed for the 109 cases interviewed.

Self-Training, Self-Optimizing Infrared Expert System

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

Program Area: *Other Occupational Needs*
Grant Number: *5 R01 OH02404-02*
Start & End Dates: *09/29/87 - 12/31/89*
Funding Level: *$114,857 ($238,744 Cum)*

Importance to Occupational Safety and Health

Real time air monitoring is central to:

1. evaluating airborne workplace hazards prior to the design, installation, and/or operation of process changes or control devices;
2. detecting sudden releases of toxic air contaminants to the workplace or the community;
3. evaluating suspected air contaminant-related adverse health effects during epidemiologic studies; and
4. conducting health hazards evaluations.

This project is aimed at developing the methodology for the rapid, direct monitoring of airborne contaminants using Fourier transform infrared (FTIR) spectroscopy, and developing software to allow the use of the method by industrial hygienists. As such, this new instrumentation will assist in the achievement of all of the above health-related goals.

Objectives

A self-training, self-optimizing expert system will be developed to identify the components of mixtures of airborne contaminants of industrial hygiene significance using infrared spectroscopy.

Methodology

1. Acquire a library of the IR spectra of organic vapors and gases of significance to industrial hygiene at certified concentrations in air.
2. Determine the spectral regions for optimal specificity and limit of detection for each compound separately and in mixtures likely to be found in workplace air.
3. Develop optimal software for the quantitation of the components of mixtures of organic vapors in air.
4. Develop optimal software for the identification of the components of mixtures of organic vapors in air.
5. Develop the expert system and self-diagnosing software tools for the use of the above system by an industrial hygienist.
6. Work with NIOSH and the EPA Environmental Response Team for evaluation of FTIR applied to actual air samples.

Significant Findings

1. Objectives 1-3 (above) have been accomplished and published. Quantitation of workplace samples from both semiconductor device manufacturing processes, and degreasing operations in metal manufacturing, have been accomplished. The latter study was performed in conjunction with the evaluation of a Foxboro MIRAN for use in the quantitation of air contaminants. In addition, a method was validated for the quantitation of CS_2 eluates of charcoal tubes by FTIR for this application.
2. Objective 4 has been accomplished, and is in the process of being automated. We had consistently failed to accomplish this objective using expert system techniques. An algorithmic method, iterative least squares fitting (ILSF) has been utilized to accomplish this objective. ILSF must now be evaluated for actual workplace air samples.
3. The above system development was accomplished on a Nicolet 1280 mini-computer using Fortran 77 language. All of the data and software are being transferred to an MS-DOS 80386/387 system, with software re-written in "C" and "CLIPS" for computing speed and flexibility. Microsoft Windows is being used as an interface between the software and the industrial hygienist. Initial improvements in speed of a factor of approximately 50 have been realized thereby. Work will continue with support from G.M. Co.

Publications

Wythoff B, Levine SP, Tomellini SA: Spectral Peak Verification and Recognition Using a Multi-Layered Neural Network. Anal Chem 62:2702-2709, 1990

Mouradian RF, Levine: Evaluation of a Nitrogen-Cooled, Electrically Heated Cold Trap

Inlet for High-Speed Gas Chromatography. In: Journal of Chromatographic Science, Vol 28, No 12, Preston Publications, pp. 643-648, 1990

Xiao HK, Levine SP, Kinnes G, Almaguer D: Evaluation of the FTIR for Analysis of TCE in the Presence of Freon 113 in Carbon Disulfide Eluates of Charcoal Air Sampling Tubes. Am Ind Hyg Assoc J 51:402-404, 1990

Xiao HK, Levine SP, D'Arcy JB, Kinnes G, Almaguer D: Comparsion of the FTIR and the MIRAN for Determination of TCE in the Presence of Freon-113 in Workplace Air. Am Ind Hyg Assoc J 51:395-401, 1990

Ying LS, Levine SP, Tomellini SA: Expert System for Interpretation of the IR Spectra of Environmental Mixtures. In: Computer-Enhanced Analytical Spectroscopy, Vol 2, (ed. HLC Meuzelaar), Plenum Publishing Corporation, pp. 245-257, 1990

Levine SP, Xiao HK, D' Arcy JB, Pritchett T, Turpin RD: FTIR Least Squares Method for Quantitative Analysis of Multi-Component Mixtures of Airborne Vapors. In: Measurement of Toxic and Related Air Pollutants, (eds. RKM Jayanty, S Hochheiser), AWMA Pittsburg, PA, pp. 895-900, 1990

Strang CR, Levine SP, Herget WF: A Preliminary Evaluation of the FTIR Spectrometer as a Quantitative Air Monitor for Semiconductor Manufacturing Process Emissions. Am Ind Hyg Assoc J 50:70-77, 1989

Strang CR, Levine SP: The Limits of Detection for the Monitoring of Semiconductor Manufacturing Gas and Vapor Emissions by FTIR Spectroscopy. Am Ind Hyg Assoc J 5:78-84, 1989

Ying LS, Levine SP, Strang CR, Herget WF: FTIR Spectroscopy for Monitoring Airborne Gases and Vapors of Industrial Hygiene Concern. Am Ind Hyg Assoc J 30:354-359, 1989

Ying LS, Levine SP: Evaluation of the Applicability of FTIR Spectroscopy for Quantitation of the Components of AIrborne Solvent Vapors. AMer Ind Hyg Assoc J 50:360-365, 1989

Ying LS, Levine SP: FTIR Spectroscopy for Monitoring Airborne Solvent Vapors in Workplace Air. Am Ind Hyg Assoc J 50(7):360-365, 1989

Ying LS, Levine SP: FTIR Least-Squares Methods for the Quantitative Analysis of Multi-Component Mixtures of Airborne Vapors of Industrial Hygiene Concern. Anal Chem 61:677–683, 1989

Xiao HK, Levine SP, D'Arcy JB: Qualitative Aspects of the Use of Iterative LSF Procedures for the Identification of Organic Vapor Mixtures by FTIR Spectrophotometry. Anal Chem 61:2708-2714, 1989

Levine SP, Ying LS, Strang CR, Xiao HK: Advantages and Disadvantages in the Use of FTIR and Filter IR Spectrometers for Monitoring Airborne Gases and Vapors of Industrial Hygiene Concern. Applied Ind Hyg 4:180-187, 1989

Ying LS, Levine SP, Strang CR: Fourier Transform Infrared (FTIR) Spectroscopy for Monitoring Airborne Gases and Vapors of Industrial Hygiene Concern. Am Ind Hyg Assoc J, accepted for publication, 1988

Ying LS, Levine SP: Fourier Transform Infrared (FTIR) Spectroscopy for Monitoring Airborne Solvent Vapors in Workplace Air. Am Ind Hyg Assoc J, in press, 1988

Ying LS, Levine SP, Tomellini S, Lowry SR: Training, Self-Optimizing Expert System for Interpretation of the Infrared Spectra of Mixtures. Anal Chem 59:2197-2203, and Anal Chem Acta 210:51-62, 1987

Halogenated Hydrocarbon Toxicity in Proximal Tubules

Joseph T. Hjelle, Ph.D.
University of Illinois
College of Medicine at Peoria
One Illini Drive, Box 1649
Peoria, Illinois 61656

Program Area: *Other Occupational Needs*
Grant Number: *5 R01 OH02417-03*
Start & End Dates: *09/01/87 – 08/31/90*
Funding Level: *$93,942 ($279,085 Cum)*

Importance to Occupational Safety and Health

Chloroform and carbon tetrachloride are environmental and occupational contaminants with documented nephrotoxic potential in humans and laboratory animals. The primary site of kidney

damage produced by these solvents is the proximal tubule.

This research project explores the toxicity of chloroform and carbon tetrachloride using proximal tubules from rabbits and humans and examines prospective *in vitro* methods for studies of nephrotoxicity. The anticipated useful information to come from this project will (1) further development of meaningful predictive *in vitro* toxicology methods using rodent and human tissues, and (2) enhance understanding of the mechanisms by which these organic solvents cause kidney damage.

Objectives

The overall aims of the project are to examine: (1) the validity of the isolated rabbit tubule model as a tool in the study of nephrotoxicants and (2) the validity of the rabbit tubule model as a predicator of nephrotoxicity in humans.

Methodology

Kidney proximal tubules are isolated from control and phenobarbital-induced rabbits by non enzymatic sieving techniques and then studied *in vitro*. Such tubules in suspension are used to (1) describe the concentration and time dependence of the solvent-induced damage during short-term incubations; (2) evaluate the role of cytochromes P-450, lipid peroxidation, and glutathione in determining the severity of damage to the tubules *in vitro*; and (3) be a source of material for studies of various enzyme systems involved in the biotransformation of these organic solvents.

Human kidneys unusable for transplantation are used to develop isolation techniques for human kidney tubules and proximal tubule cells. Human kidney tissue is used to examine (1) viability of these human cells *in vitro* (including tissue culture), (2) enzyme activities of potential significance, and (3) the usefulness of human kidney cells *in vitro* in studies of organic solvent toxicity.

Significant Findings

Rabbit kidney proximal tubules were readily obtained in good yield and high purity from both control and drug-treated animals. The tubules in suspension were viable for up to 8 hours. When exposed *in vitro* to chloroform or carbon tetrachloride, tubules demonstrated both a concentration and time-dependent loss of viability as assayed by release of lactate dehydrogenase (LDH). Unfortunately, loss of LDH activity occurred at solvent concentrations too high to be of relevance to most human exposures. None of the other potential indices of cell viability (organic acid secretion, oxygen consumption, and release of membrane bound enzymes) examined to date are more sensitive than LDH release. Solvent-induced cell damage was confirmed by electron microscopy. Tubules from the phenobarbital-treated animals were no more sensitive to solvent-induced toxicity than the tubules obtained from non-treated animals. Although the tubules accumulated glutathione (GSH) *in vitro,* solvent-induced release of LDH was not appreciably altered by pre-loading the cells with GSH.

When human kidneys were used, neither purely mechanical nor a combination of mechanical and enzyme digestion procedures yielded sufficient quantities of viable tubule segments. In an attempt to obtain tubules from kidneys with less connective tissue, kidneys from two patients with polycystic kidney disease (PKD) were used; only microdissection or enzyme digestion with mechanical stress gave tubule segments. These segments and cells were subsequently identified as being from collecting tubules. Thus, in our hands, use of isolated human kidney tubules for large scale toxicity testing has been unsuccessful.

The use of tissue cultured cells may provide a better approach to the study of long-term, low-concentration exposures to organic solvent toxicity. Rabbit proximal tubule cells were propagated in tissue culture and characterized by cytochemical and ultrastructural techniques. Use of this system has enabled the detection of changes in cell function and ultrastructure at nanomolar levels of organic solvents in contrast to the millimolar levels required when using LDH release from suspended tubules. In this regard, proximal tubule suspensions (no solvent exposure) averaged 4.4 nMoles GSH/mg protein (S.D.=1.1; n=34); tubule cells grown in plastic dishes gave 10 nMoles GSH/mg protein (S.D.=4.7; n=40), but cells grown on permeable membranes exhibited 38 nMoles/mg protein (S.D.=4.7; n=63). The GSH levels of tubule cells grown on permeable membranes declined to 19 (S.D.=4.2; n=26) and 24 (S.D.=3.9; n=36) nMoles GSH/mg protein when exposed to 9.27 nMoles $CHCl_3$ and 229 nMoles CCl_4, respectively. For reference, human kidney cortex exhibited 6-9 nMoles GSH/mg protein; rabbit kidney cortex and isolated tubules exhibited 10-15 and 4-7 nMoles GSH/mg protein, respectively. Transcellular electrical resistance of tubule cells on membranes fell from a 1097 Ohms cm^2 (n=69) to a low of 865 Ohms cm^2 after exchange of culture medium; within two hours exchange, the resistance returned to 984 Ohms cm^2. In contrast, cells exposed to 9.27 nM $CHCl_3$ fell from 1116 Ohms

cm^2 to 566 Ohms cm^2; after two hours, resistance had returned only to 769.8 Ohms cm^2 (n=34). Exposure of cells to 229 nMole $CC1_4$ resulted in a fall from 1060.8 Ohms cm^2 to 646.8 Ohms cm^2, and after two hours incubation, a recovery to 978 Ohms cm^2 (n=69). By electron microscopy, tubule cells on plastic when incubated with the same concentrations of solvents as above for two hours exhibited substantial blebbing at the cell surface; such blebbing was rarely observed in the absence of solvent. Confluent cell cultures exhibit an electrical resistance, specific lectin staining, ultrastructure, and organic acid transport consistent with retention of at least some aspects of proximal tubule structure and function. Thus, cultured proximal tubule cells may represent a sensitive *in vitro* system for studies of organic solvent toxicity.

Publications

Hjelle JT, Waters DC, Golinska BT, Steidley KR, Burmeister V, Caughey R, Ketel B, McCarroll DR, Prior RB, Miller MA: Autosomal Recessive Polycystic Kidney Disease: Characterization of Human Peritoneal and Cystic Kidney Cells *In Vitro*. American Journal of Kidney Disease 15:123-136, 1990

Hjelle JT, Guenthner TM, Bell K, Whalen R, Fluoret G, Carone FA: Inhibition of Catalase and Epoxide Hydrolase by the Renal Cystogen 2-amino-4,5-diphenylthiazole and its Metabolites. Toxicology 60:211-222, 1990

Permeation of Glove Materials by Organic Solids

James K. Hardy, Ph.D.
University of Akron
College of Arts and Sciences
Department of Chemistry
Akron, Ohio 44325

Program Area: *Other Occupational Needs*
Grant Number: *5 R01 OH02651-02*
Start & End Dates: *06/01/89 - 05/31/91*
Funding Level: *$39,242 ($89,050 Cum)*

Importance to Occupational Safety and Health

The exposure of unprotected hands to solid organic chemicals can result in various injuries via dermal absorption. Glove materials used to protect the skin from direct contact may allow chemicals to permeate, creating conditions hazardous to human health. To provide optimum worker protection, methodology must be developed to evaluate the critical permeation characteristics of breakthrough time, steady-state permeation rate, and steady-state permeation time. By evaluation of a representative set of chemicals, glove materials, and exposure conditions, it should be possible to determine what effect chemical vapor pressure and relative solubility have on the permeation characteristics. Furthermore, the availability of this information will aid in selection of optimum gloves and development of improved glove materials.

Objectives

The objective of this study is to develop a method for the evaluation of the permeation behavior of five protective glove materials when exposed to organic compounds using a representative set of 13 chemicals. Variations in this behavior will be evaluated over a range of from 0 - 40°C using material thicknesses of from 0.15 - 0.6 mm. This information will then be related to the vapor pressures for the materials and the relative glove/chemical solubilities. This information should aid in predicting the effective protection for unevaluated glove/chemical pairs. Permeation will also be evaluated over a range of humidities and with simulated perspiration as the collecting medium to more accurately reflect actual exposure conditions.

Methodology

A glove sample of known thickness is placed between two halves of a permeation cell. A helium flow is directed through one side of the cell, then through a gas sampling loop on a 10-port valve, and then to a flame ionization detector of a gas chromatograph. After a stable detector baseline is observed, a pellet of the chemical to be evaluated is placed in contact with the outer surface of the membrane, and the detector response is monitored and stored on a computer. The response curve is monitored and when steady state has been reached, the position of the valve is changed which causes an injection of the chemical onto a chromatographic column. The resulting peak is quantified by comparison to a standard and then related to the response at the time of injection for the permeation curve. This allows for the determination of the steady-state permeation rate (SSPR) and detection limit at breakthrough. Breakthrough time is determined based on the first observation of a

response greater than twice the signal-to-noise ratio with no return below the base line. The effect of temperature on SSPR is evaluated by placing the permeation cell in the chromatographic oven. Through the use of a CO_2 cryogenic cooler, temperatures over a range of from 0 - 40°C can be produced to +/- 0.1°C accuracy. Steady state is initially achieved at the upper temperature limit and the effect of temperature is determined by evaluating variations in response while cooling the cell using a temperature ramp of -0.1°C/min.

Significant Findings

The permeation cell has been constructed and the general method evaluated. A Hewlett - Packard 5890 series II gas chromatograph equipped with an FID detector, 10-port sampling valve, and cryogenic cooler has been interfaced to the cell using a 200-cm heated transfer line. Data collection and analysis is accomplished using a Hewlett - Packard Pascal GC ChemStation and procedures have been written using the system's macro language to aid in the interpretation of permeation curves. To date, room temperature evaluation of single thickness (5 ml) of 5 glove materials has been conducted for permeation by 9 chemicals. The results are summarized in Tables I and II, where BT = breakthrough time and SSPR is the steady-state response rate in units of μg/min/cm2.

Table I. Breakthrough times in minutes.

Permeant	Glove Materials				
	A	B	C	D	E
1	8.5	9.6	18.5	45.0	ND
2	4.3	4.7	11.5	19.0	41.3
3	5.2	5.4	3.6	6.4	9.5
4	7.0	8.1	138.0	14.2	ND
5	3.5	4.8	ND	475.0	420.0
6	10.4	10.6	28.0	21.0	185.0
7	2.4	3.5	11.0	31.5	39.5
8	4.5	5.2	ND	ND	ND
9	6.1	6.9	7.1	35.0	142.0

ND = no detectable breakthrough in 650 minutes

Table II. Steady state permeation rates (μg/min/cm^2).

Permeant	Glove Materials				
	A	B	C	D	E
1	0.715	0.749	0.865	0.412	ND
2	0.299	0.834	0.345	0.230	0.419
3	2.108	1.305	1.228	0.441	0.408
4	5.350	7.304	0.555	0.215	ND
5	0.304	0.344	ND	0.394	0.349
6	0.368	0.574	0.934	0.258	1.756
7	0.747	0.808	0.641	0.441	0.376
8	0.418	0.654	ND	ND	ND
9	0.585	0.591	0.487	0.445	0.323

ND = No detectable permeation within 650 minutes.

Permeant	Glove Material
1 = benzoquinone	A = Latex
2 = naphthalene	B = PVC
3 = dichlorobenzene	C = Polyurethane
4 = p-nitrotoulene	D = Neoprene
5 = camphor	E = Nitrile
6 = phenol	
7 = hydroquinone	
8 = 4,6-dintro-o-cresol	
9 = 2,4-dinitrotoluene	

No clear cut trend exists between the vapor pressure of a permeant and its breakthrough time or steady state permeation rate for any glove material. At present, temperature and vapor phase studies are being conducted to determine the relative significance of diffusion and solubility on the permeation process.

Publications

Fricker CM, Hardy JK: Method for the Evaluation of Protective Glove Materials for Permeation by Organic Solids. Proc of 199th National Meeting, American Chemical Society, Boston, MA, April 1990

Selective Real-Time Detection of Olefin Gases and Vapors

Edward T. Zellers, Ph.D.
University of Michigan
School of Public Health
Department of Environmental and Industrial Health
109 South Laboratory
Ann Arbor, Michigan 48109-2029

Program Area: *Other Occupational Needs*
Grant Number: *5 R01 OH02663-02*
Start & End Dates: *09/01/89 – 08/31/92*
Funding Level: *$87,444 ($182,933 Cum)*

Importance to Occupational Safety and Health

The chemicals chosen for study have been associated with carcinogenic, neurotoxic, and/or adverse reproductive health effects. Due to the presence of other organic-vapor contaminants in industrial settings where these chemicals are used, real-time measurement of airborne concentrations with current personal direct-reading instruments is often not possible. The sensitivity and selectivity provided by the proposed microsensor-based instrument will permit collection of more accurate personal exposure data for each of the target olefin gases and vapors.

Objectives

The goal of this research is to develop microsensor-based instrumentation for selective real-time measurement of each of a series of olefin gases and vapors in the presence of common olefin and non-olefin industrial co-contaminants. The primary focus will be on the detection of styrene, ethyl acrylate, acrylonitrile, butadiene, β-chloroprene, vinyl chloride, and vinylidene chloride. Data relevant to monitoring other toxic olefins will also be obtained. The instrument will employ one or more surface-acoustic-wave (SAW) oscillators or resonators as the sensing element(s). Selectivity for a given target olefin will be achieved by coating the sensor surface with one of several regenerable trapping agents.

Methodology

A series of trapping agents will be synthesized and tested for reactivity with each of the target olefins. The trapping reagents will comprise several platinum-olefin coordination compounds of the general formula trans-$PtCl_2$(amine)(olefin), and related polymer-bound compounds, designed to react (via substitution of the initially bound olefin) specifically with the target olefin. Subtle changes in the electronic and steric properties of the amine and olefin ligands in the reagent should allow for optimization of selectivity toward each of the target olefins in the presence of other potentially interfering chemicals. It is expected that post-exposure regeneration of the original trapping reagents will be possible *in situ* by simple chemical treatment. The coated sensor(s) will be incorporated into a compact prototype instrument equipped with data-storage and digital-readout capabilities for both real-time and time-weighted-average measurements. Instrument performance will be evaluated in the laboratory with respect to several relevant operating parameters.

Significant Findings

Real-time measurement of low-ppm concentrations of styrene vapor in the presence of each of several olefin and non-olefin solvent vapors has been achieved using a 30-MHz SAW sensor coated with a mixture of trans-$PtCl_2$(ethylene)(pyridine) and poly(isobutylene). The response of this coated sensor to each of several other olefins has also been investigated. For example, ethyl acrylate (EA) can be selectively detected in the presence of other acrylate monomers (e.g., methyl crotonate (MC) and methylmethacrylate (MMA)), vinylidene chloride, and several non-olefin vapors (e.g., ethyl acetate, methanol, THF, toluene, hexane, methanol, acetone, and chloroform). The limit of detection for EA is about 5 ppm for operation at 40°C (note: an increase of 5-fold or greater in sensitivity is expected with the higher frequency SAW sensors to be used in future tests).

The observed selectivity for EA over MC and MMA is thought to be due to the presence of the methyl groups on the double bonds in MC and MMA. Consistent with this trend, we have found responses for a series of butenes in the order 1 butene > cis-2-butene > trans-2-butene, and no measurable responses for isobutylene and 2,3-dimethyl-2-butene. Limits of detection for the first three olefins range from about 5-60 ppm with the sensor operating at 40°C. Similar trends are observed in a series of aromatic olefins, with responses in the order: styrene > beta-methylstyrene >> alpha-methyl styrene ~ indene.

To determine the extent of steric effects in the trapping agent, a series of methyl-substituted pyridine ligands have been examined. For all of the olefins tested, the same trends in the magnitudes of the responses are observed: pyridine ~ 4-methylpyridine > 2-methylpyridine >> 2,6-dimethylpyridine. We have found, however, that the magnitudes of the differences in the responses to these trapping agents vary with each olefin. This may provide a means of differentiating between these olefins if different coatings were used simultaneously in a sensor array. Experiments have also been performed with trapping agents containing 4-substituted pyridines having a range of electron withdrawing/donating strengths. Results for styrene, ethyl acrylate and vinyl acetate show very large differences in responses, depending on the nature of the 4-substituent.

Publications

Zellers ET, White RM, Rappaport SM: Use of Surface-Acoustic-Wave Sensor to Characterize the Reaction of Styrene Vapor with a Square-Planar Organoplatinum Complex. Anal Chem 62:1222-1227, 1990

Zellers ET, Noralynn H, White RM, Rappaport SM: Selective Real-time Measurement of Styrene Vapor Using a Surface-Acoustic-Wave Sensor with a Regenerable Organoplatinum Coating. Anal Chem 62:1227-1232, 1990

Theory and Evaluation for a Workplace FTIR-ROSE Monitor

Steven P. Levine, Ph.D.
University of Michigan
School of Public Health
Department of Environmental and Industrial Health
1420 Washington Heights
Ann Arbor, Michigan 48109-2029

Program Area: *Other Occupational Needs*
Grant Number: *5 R01 OH02666-02*
Start & End Dates: *09/01/89 - 08/31/91*
Funding Level: *$153,098 ($301,673 Cum)*

Importance to Occupational Safety and Health

Air monitoring instruments for "remote sensing of emissions" (ROSE) have, for the past 20 years, held out the promise of monitoring systems that could "look across" environmental sampling sites or the workplace and "see" the air contaminants. The first ROSE Fourier Transform Infrared (FTIR) system was described around 1980.

More recently, the use of FTIR, without remote sensing, but instead with the use of a closed gas cell into which the sample is pumped, has been explored for both automotive exhaust and workplace air samples. Using classical least squares fit (LSF) data analysis methods, the FTIR was proven by our group to be applicable to the quantitative analysis of air samples.

In the last few years, several groups have begun experimentation with ROSE-FTIR, including the U.S. Army for remote sensing of chemical warfare agents. EPA-sponsored groups have used ROSE-FTIR and differential absorption laser (DIAL) systems for remote sensing of pollutants at hazardous waste sites, and potentially for fenceline emergency chemical-release monitoring. The first such study at a hazardous waste site was performed by our group. More recently, a theoretical modelling paper was published that described how a remote sensing instrument might be used to advantage in a workplace where the concentration gradients of air contaminants would be constant over the time scale that it would take to "crisscross" the workplace with beams.

Objectives

During the first year of our two-year, NIOSH-sponsored study, we have addressed the questions of ROSE-FTIR instrument use: (1) under conditions simulating the workplace (in the Berkeley environmental chamber); and (2) in the workplace (at Abbott Pharmaceutical Laboratories).

All of these tests have been directly related to the situation where there is a: (1) slowly varying analyte concentration; and (2) path-weighted average ROSE beam results are correlated with time-weighted average continuous monitor results.

The objective of the grant is to evaluate this laboratory and field data, and thereby develop a model for the use of the ROSE-FTIR, and all optical beam systems, for workplace air monitoring.

Methodology

Tests of the transportable ROSE-FTIR system were performed at General Motors Research Center in an exposure chamber in which temperature, humidity, and air contaminant concentration could be tested; at the University of California, Berkeley, in a large exposure room in which air contaminant concentration could be modeled with the aid of a 3-D sonic anemometer and monitored using the IR beam and a multi-point conventional monitor. In addition, a field trial was performed at Abbott Pharmaceutical Laboratories, Chicago, IL.

Significant Findings

1. The ROSE-FTIR system was activated and tested for the first time, and operators were trained. It was first tested at General Motors Research Center, and then shipped to Berkeley for tests that have formed the heart of this study.
2. The LSF software has been modified to take into account the presence of non-analyte contaminants in the background spectra.

3. The exposure chamber at General Motors Technical Center was used to assess the stability of the FTIR-ROSE system to variations in temperature (15-35° C) and relative humidity (20-85%) in a contaminant-free environment. In addition, the accuracy of the FTIR-ROSE system in the quantitation of certain target analytes (methanol, ozone, and a complex mixture of solvents) was tested over portions of that temperature and humidity range. Data analysis is as yet incomplete. However, instrument stability does not appear to be a problem if sufficient attention is paid to obtaining suitable spectra of background air.
4. The activation and optimization of the 5150 ft^3 ventilation chamber located at the University of California Richmond Field Station was accomplished for the evaluation of the ROSE FTIR: (a) The chamber, vapor generator, anemometer, multi-point monitor, and FTIR-ROSE system performed as well as or better than optimal manufacturer's specifications. (b) The beam average concentration obtained from the ROSE-FTIR and the path average concentration from the THC line array were in close agreement. This is the expected result. (c) The FTIR response for multiple mirror geometries increased in direct proportion to the beam path length.
5. A preliminary test of the ROSE-FTIR was undertaken under actual workplace conditions at Abbott Pharmaceutical Laboratories. The work was designed to parallel as much as possible the simulation experiment in the chamber at Berkeley, while presenting a complex mixture of organic vapors to the instrument. Data evaluation will take place during year 02 of this grant.

Company Characteristics and Medical Screening of Workers

Leslie I. Boden, Ph.D.
Boston University School of Medicine
80 East Concord Street
Boston, Massachusetts 02118-2394

Program Area: *Other Occupational Needs*
Grant Number: *1 R01 OH02739-01*
Start & End Dates: *09/01/90 – 08/31/91*
Funding Level: *$48,535 ($48,535 Cum)*

Importance to Occupational Safety and Health

Workplace characteristics like wages, unionization, turnover, and firm size do not directly influence worker health but can affect the value to employers of medical screening. Employers may choose whether to screen to maximize the benefits to them. However, such a decision may not be beneficial to the health of the screened workers and may largely shift the costs of illness to the workers or other employers, thus reducing the incentive to reduce workplace hazards.

Objectives

The long-term objective of this research is to identify the extent of excessive medical screening, so that, if needed, appropriate public policies can be designed.

Methodology

The proposed research uses data from two national studies that provide information on potential exposure to workplace hazards, the prevalence of several types of medical screening, unionization, firm size, and turnover (the NOHS and NOES), as well as industry-specific data on wages and turnover. Logistic regression analysis will be employed to estimate the association of wages, unionization, turnover, and firm size with the prevalence of medical screening, controlling for workplace occupational health risks.

Significant Findings

None to date.

Peripheral Markers of Muscarinic Receptors

Lucio G. Costa, Ph.D.
University of Washington
Department of Environmental Health, SC-34
Seattle, Washington 98195

Program Area: *Other Occupational Needs*
Grant Number: *5 K01 OH00054-03*
Start & End Dates: *09/29/86 – 03/31/90*
Funding Level: *$32,300 ($97,100 Cum)*

Importance to Occupational Safety and Health

These studies are providing relevant data on the characteristics of muscarinic receptors on lymphocytes and on their modulation by cholinergic agents. The finding that similar alterations can be detected in brain and lymphocytes of animals exposed to cholinergic agents and to organophosphorus pesticides suggests that these peripheral measurements might be useful for monitoring alterations of the cholinergic system in solid tissues. This may be useful in the detection of toxic effects due to occupational exposures, or in the identification of workers who might be particularly sensitive to chemicals acting on the cholinergic system.

Objectives

This project tests the hypothesis that muscarinic receptors on circulating lymphocytes could represent a marker of the same receptors in the CNS, the lung, and other solid tissues; and that alterations of muscarinic receptors in such tissues due to environmental or genetic factors, to pharmacological treatment, or to chemical exposure, will be detected by measuring receptor density, affinity, and function in lymphocytes.

Methodology

Studies on muscarinic receptors on lymphocytes were conducted using ^{3}H-quinuclidinyl benzilate (^{3}H-QNB) using a mixed population of lymphocytes isolated from rat spleen. The spleen was chosen for the initial characterization since a larger amount of cells can be obtained from one animal (as compared to isolating lymphocytes from blood). In further experiments, lymphocytes isolated from rat and human blood have also been utilized. Modulation of brain and lymphocyte muscarinic receptors has been studied *in vitro* and *in vivo* in rats treated with cholinergic drugs (oxotremorine, atropine) or an organophosphate insecticide (disulfoton).

Significant Findings

An extensive series of experiments were performed to characterize the pharmacological specificity of the binding site for ^{3}H-QNB, and a large number of cholinergic and noncholinergic drugs were tested for their ability to inhibit specific binding of ^{3}H-QNB. These studies indicated that the muscarinic cholinergic binding site on lymphocytes had the same pharmacological characteristics as that in brain tissues, with, however, a much lower affinity for muscarinic antagonists. Experiments with circulating lymphocytes from rats and humans confirmed the results obtained with lymphocytes isolated from the spleen.

We also showed that prolonged exposures to cholinergic compounds *in vitro* and *in vivo* modulate muscarinic receptor binding in lymphocytes as well as in brain tissue. Exposure of rat splenic lymphocytes *in vitro* to oxotremorine caused a time- and concentration-dependent decrease in the density of ^{3}H-QNB binding sites. This decrease occurred only when incubation with oxotremorine was carried out at 37°C and not at 0-4°C, suggesting that it was not an artifact due to residual, unwashed, oxotremorine. The effect of oxotremorine was mimicked by two other cholinergic agonists, acetylcholine, and carbachol, and was antagonized by atropine, which when present alone, caused an increase in ^{3}H-QNB binding. *In* vivo exposures to oxotremorine or atropine (both at 20 mg/kg/day for 14 days via an ALZA minipump) caused a significant decrease (20-30%) and increase (13-30%), respectively, of ^{3}H-QNB binding in various brain areas as well as circulating lymphocytes. Repeated administrations of the organophosphorus insecticide disulfoton (2 mg/kg/day for 14 days, ip) caused significant reductions (59%-88%) of acetylcholinesterase activity in brain, lymphocytes, plasma, and red blood cells, as well as a 23-39% decrease in brain areas and circulating lymphocytes. These results indicate that muscarinic receptors on lymphocytes and in brain tissues can be modulated by cholinergic drugs in a similar manner, suggesting that lymphocytes might be used as markers for cholinergic muscarinic receptors in nerve tissue.

Publications

Costa LG, Kaylor G, Murphy SD: *In Vitro* and *In Vivo* Modulation of Cholinergic Muscarinic Receptors in Rat Lymphocytes and Brain by Cholinergic Agents. Int J Immunopharmacol, Vol 12, No 1:67-75, 1990

Costa LG, McDonald BE, Murphy SD, Omenn GS, Richter RJ, Motulsky AG, Furlong CE: Serum Paraoxonase and Its Influence on Paraoxon and Chlorpyrifos-oxon Toxicity in Rats. Toxicol Appl Pharmacol 103:66-76, 1990

Maier WE, Costa LG: Na^+/K^+-ATPase in Rat Brain and Erythrocytes as a Possible Target and Marker, Respectively, for Neurotoxicity: Studies with Chlordecone, Organotins, and Mercury Compounds. Toxicol Lett 51:175-188, 1990

Costa LG: The Phosphoinositide/Protein Kinase C System as a Potential Target for Neurotoxicity. Pharmaceut Res Vol 22, No 4:393-408, 1990

Costa LG, Kaylor G, Murphy SD: Muscarinic Cholinergic Binding Sites on Rat Lymphocytes. Immunopharmacology 16:139-149, 1988

Costa LG: Pharmacological Modulation of Brain Nicotinic Binding Sites. In Nicotinic Acetylcholine Receptors in the Central Nervous System (eds. F Clementi, C Gotti, E Sher), Springer-Verlag, Heidelberg, pp 299-316, 1988

Costa LG: Interactions of Neurotoxicants with Neurotransmitter Systems. Toxicology 49:359–366, 1988

Costa LG: Peripheral Models for the Study of Neurotransmitter Receptors. Their Potential Application to Occupational Health. In Occupational and Environmental Chemical Hazards (eds. V Foa, EA Emmett, M Maroni, A Colombi), Ellis Horwood Ltd, Chichester, UK, pp 524-528, 1987

Costa LG: Specific Binding of ^{3}H-Methyl Scopolamine to Glass Fiber Filters. J Pharm Pharmacol 39:239-240, 1987

Costa LG, Richter RJ, Murphy SD, Omenn GS, Motulsky AG, Furlong CE: Species Differences in Serum Paraoxonase Correlate with Sensitivity to Paraoxon Toxicity. In Toxicology of Pesticides: Experimental, Clinical, and Regulatory Aspects, (ed. LG Costa), Springer-Verlag Berlin Heidelberg, pp 263-266, 1987

Minimizing Dermal Exposure to Pesticides in Greenhouses

Richard A. Fenske, Ph.D.
Rutgers University
Department of Environmental Sciences
P.O. Box 231
New Brunswick, New Jersey 08903

Program Area: *Other Occupational Needs*
Grant Number: *5 K01 OH00063-03*
Start & End Dates: *05/01/87 - 04/30/90*
Funding Level: *$32,230 ($96,655 Cum)*

Importance to Occupational Safety and Health

Greenhouse applicators are likely to receive substantial dermal exposure during the spraying of pesticides. Few studies have characterized such exposure patterns carefully. The use of a fluorescent tracer allows visualization of exposure patterns and can assist both investigators and workers in determining the causes of exposure and the means for reducing such exposures. It is important to identify factors unique to greenhouse applications which affect dermal exposure.

Objectives

1. Identify the major variables influencing exposure during pesticide handgunning applications in greenhouses.
2. Evaluate the performance of protective clothing under normal application conditions.
3. Determine the effect of ventilation on dermal exposure during applications.
4. Determine the ability of a visual scoring system of fluorescent tracer deposition patterns to accurately categorize worker exposure.
5. Determine the ability of fluorescent tracer evaluation to serve as an educational tool in reducing dermal exposures.

Methodology

A fluorescent tracer is introduced into pesticide spray mixes prior to application. Workers conduct normal application activities and are subsequently examined under longwave ultraviolet light in a mobile laboratory. Patterns of dermal fluorescence are detected and quantified by a video imaging system. An exposure score is assigned based on visual observations. Key factors believed to influence dermal exposure are varied under controlled conditions; e.g., ventilation system and type of protective garment worn. Dermal patches are attached to the inside and outside of clothing to provide an evaluation of spray deposition and clothing penetration independent of the imaging system and visual observation. These patches are extracted in the laboratory, and levels of the fluorescent tracer are determined by fluorometry.

Significant Findings

The most significant findings to date are as follows:

1. Clothing normally designated as "chemical-resistant" can experience substantial breakthrough within a one-hour application

period if the worker wets the clothing by direct contact with treated foliage.
2. Ventilation systems which produce directional air movement reduced aerosol deposition on skin surfaces substantially during high pressure (200 psi) spraying when applications were conducted by well-trained workers (compared to applications with no ventilation). Exposure was not reduced and in some cases increased when applications were conducted by untrained workers.
3. The ability to see exposure patterns through fluorescent tracer visualization led workers and greenhouse managers to adopt more careful pesticide use practices, e.g., greater care in handling and application and purchase of appropriate protective garments.

Hepatic Steatosis and Solvent: A Case-Control Study

Michael J. Hodgson, M.D.
University of Pittsburgh
School of Medicine
190 Lothrop Street #149
Pittsburgh, Pennsylvania 15261

Program Area: *Other Occupational Needs*
Grant Number: *5 K01 OH00071-02*
Start & End Dates: *09/29/87 - 09/28/90*
Funding Level: *$26,852 ($56,427 Cum)*

Importance to Occupational Safety and Health

Liver disease is the tenth leading cause of death and the ninth leading cause of years of potential life lost before the age of 65. Although documented and potential hepatotoxins are frequently used in the U.S., outbreaks of occupational liver disease occur only infrequently. Sporadic cases of toxic liver disease are recognized only rarely. Other risk factors, such as obesity and diabetes, have been implicated, although cause of relationships are as yet unclear. Physicians are generally unaware of the various risk factors, unaware of implications of work exposures, and unaware of appropriate diagnostic or therapeutic consequences.

Objectives

1. To estimate the risk for liver disease resulting from alcohol, obesity, and solvent exposures.
2. To develop educational materials for practicing physicians.

Methodology

Case-control study of fatty liver disease (FLD)

Population: all cases of fatty liver disease referred to seven gastroenterology groups in Allegheny County over a two-year period with biopsy-proven FLD were eligible. As controls, age- (within five years) and gender-matched controls were selected from participating GI clinics.

Exposure assessment: Alcohol consumption, obesity, and solvent use were quantified for four time points, i.e., at examination, at diagnosis, maximum usual consumption, and average. Solvent exposure was quantified with ordinal scales of frequency, intensity, and duration. Specific exposures to pesticides, drycleaning fluids, paint strippers, and spot removers were also identified.

The study was terminated prematurely because individuals with FLD by sonogram or CT scanning techniques were potentially no longer being biopsied unless they had exposures identified. Apparently, biopsy habits in the gastroenterology community have changed. The study was discontinued to prevent ascertainment bias, and the last two cases were discarded.

Statistical Analysis: Statistical methods for matched data were used.

Case-control study of risk factors for liver disease

Population: all cases of liver disease seen by one physician at a university hospital from 1/1/88 to 12/31/88 were selected independent of diagnosis. Two control series were identified, both matched on age (within five years) and gender. A first series was selected from university GI clinics and a private gastroenterologist with a similar demographic profile of patients. A second series was obtained by random digit dialing.

Exposure assessment: Alcohol consumption, obesity, and solvent use were quantified for four time points, i.e., at examination, at diagnosis, maximum usual consumption, and average. Solvent exposure was quantified with ordinal scales of frequency, intensity, and duration. Specific exposures to pesticides, drycleaning fluids, paint strippers, and spot removers were also identified.

Statistical Analysis: Statistical methods for matched data are being used.

Re-analysis of NHANES II data

To test the importance of the identified risk factors in a population-based study, the NHANES data set is being analyzed to examine the influence of obesity, recent and chronic alcohol consumption, diabetes, and occupational exposures on liver function.

Exposure assessment: Usual coded data from NHANES were used, including body mass index (weight/height squared), diabetes (questionnaire definition), recent and usual alcohol consumption in ounces per week, and occupation. Occupations were coded as exposed/unexposed on the basis of a review of the literature and occupations identified from the case-control studies.

Statistical analysis: Statistical methods for cross-sectional data are being used.

Significant Findings

A case-control study suggested that obesity and occupational exposure to animal hepatotoxins (OR = 4.5) were independent risk factors for the development of fatty liver disease. No evidence for multiplicative interaction was documented in logistic models. This may have to do with the relatively small sample size or with the lack of such an interaction. When the variable "alcohol consumption" was re-coded from a value of "4 ounces per day" to "any alcohol," alcohol consumption per se constituted a third independent risk factor.

Anecdotal evidence (case series) suggests that 1,1,1-Trichlorethane should be reconsidered as a potential human hepatotoxin.

Chronic Liver Disease

Not yet available.

NHANES Data

Not yet available.

Publications

Hodgson MJ, Heyl A, Van Thiel DH: Liver Disease Associated with Exposure to 1,1,1-Trichlorethane. Archives of Internal Medicine 149:1793-1798, 1989

Hodgson MJ, Van Thiel DH, Lauschus K, Karpf M: Liver Disease in Hazardous Waste Workers: The Role of Obesity. Journal of Occupational Medicine 31:238-242, 1989

Hodgson MJ, Goodman-Klein B, Van Thiel DH: Evaluating the Liver. In: Medical Surveillance in Hazardous Waste Workers, (ed. M Gochfeld), State-of-the-Art Reviews in Occupational Medicine 5:67-78, 1989

Hodgson MJ, Van Thiel DH: Gastrointestinal Disease. Control of Occupational Disease in Man, (eds. B Levy, G Wagner, E Baker), APHA Monograph, in press, 1989

Hodgson MJ: Occupational Liver Disease–A Case Work-up. Cases Studies in Occupational Disease, (ed. R Sokas), in press, 1989

Ethical Decision-Making in Occupational Settings

Bonnie Rogers, Dr.P.H.
University of North Carolina
School of Public Health
CB #7400
Chapel Hill, North Carolina 27599

Program Area: *Other Occupational Needs*
Grant Number: *5 K01 OH00072-03*
Start & End Dates: *04/01/88 - 03/31/91*
Funding Level: *$32,369 ($97,161 Cum)*

Importance to Occupational Safety and Health

It is well known that workers are exposed to a variety of occupational hazards (e.g., biological, chemical, and physical hazards) and many of these workers, i.e., pregnant women, may be particularly vulnerable. Issues related to risk of exposure to hazardous substances, right-to-know, workplace discrimination, screening without informed consent, invasion of privacy, lack of confidentiality, whistleblowing, use of incentives to entice the worker to accept risk, and lack of providing adequate protective equipment are but a few problems that create ethical issues for health care professionals. This study has identified several ethical dilemmas that occupational health nurses (OHNs) find themselves grappling with, but without satisfactory resolution. Decisions regarding these problems have far reaching consequences for the health and well-being of the American workforce. Recognition of ethical problems and development of appropriate actions within an ethical framework will help guide policy development at all levels. In addition, discussion of these issues and approaches should be encouraged within occupational health curricula.

Objectives

The purposes of the proposed research are: (1) to identify and develop an inventory of recurrent ethical dilemmas experienced by occupational health nurses; (2) to develop and administer an instrument to measure occupational health nurses' actions responsive to each dilemma; and (3) to determine if specific variables, i.e. type of employment, work experience, educational level, support systems, and previous familiarity with the ethical dilemmas are associated with nurse responses to dilemmas. The ultimate goal of this research is to identify nursing actions which are beneficial to workers in helping to resolve ethical dilemmas in occupational health.

Methodology

Phase I, the descriptive study (completed), was designed to develop and provide an inventory of recurrent ethical dilemmas experienced by a representative sample of practicing OHNs through use of a four-round Delphi technique. Identified dilemmas were categorized by a nurse ethicist to delineate recurrent dilemmas and then rated by OHNs as to the importance and impact of the dilemma.

In Phase II (completed), practicing OHNs representing geographic regions of the country developed nursing actions responsive to each ethical dilemma. These actions were evaluated, by nurse ethicists, as to their relative congruence with the Code of Ethics. An instrument containing the ethical dilemmas and nursing actions was pilot tested on nearly 40 OHNs representative of large/small industries and hospitals for reliability, validity, and clarity. Subjects were asked to specify actions as being both realistic and ideal.

In Phase III, the instrument was administered nationally to more than 300 practicing OHNs to measure their responses to ethical dilemmas. Descriptive analyses of nursing actions across dilemmas will be provided. Responses will be analyzed on demographic/employment variables identified and on actions as idealistic versus realistic behaviors. Information will be disseminated through publications and conferences.

Significant Findings

Phase I of the study, identification of the most pressing and recurrent ethical dilemmas in occupational health settings experienced by OHNs, has been completed through use of a four-round Delphi technique procedure. In this phase, nearly 400 descriptions were received from 137 respondents. A consensus on concerns of the most important problems was reached. Ethical dilemmas were categorized by nurse ethicists from the incidents themselves, from the general bioethics literature, other surveys of ethical problems/dilemmas in nursing, and the Code for Nurses.

The categorical placement of the dilemmas sometimes fell under more than one category. An example would be situations that could be categorized as both "right-to-know" and "truthtelling" or an underlying concern for avoiding/preventing harm and respecting autonomy. These were categorized according to what was considered to be the primary ethical problem. Dilemmas were categorized into the following areas: Interests/Welfare of Individual vs. Interest/Welfare of Group or Company; Truthtelling/Lying, Deception; Respect of Autonomy; Justice and Equity; Employee vs. Employer Right-to-Know; Incompetent, Unethical, Illegal Practice of Health Care Professionals; Protection of Confidentiality/Respect for Privacy; Whistleblowing; and Loyalty/Obligation to Employer. Using these categorical themes, an instrument was designed which contained 48 recurrent ethical dilemmas representing these categories. Utilizing the Delphi procedure, the 48 ethical dilemmas were rated on three successive rounds and group means were calculated for each variable, importance to the profession, and impact on worker health.

In Phase II of the study, the scores for the 48 ethical dilemmas were reaveraged and dilemmas with combined average scores (for importance to the profession and impact on worker health) of at least 6.00 (on a 7.00 scale) were determined to be the most pressing problems. This resulted in a total of 20 ethical problems to be used in the Phase II Ethics Workshop held in Chapel Hill, North Carolina on November 9-11, 1989. Nineteen individuals participated in the workshop to discuss and develop alternative strategies to address the dilemmas. Final strategies were developed for each dilemma discussed, and an instrument to measure nursing actions was developed for each of the 20 dilemmas. Dilemmas and strategies developed were then rated by nurse ethicists as to appropriate ethical responses.

In Phase III, all dilemmas were pilot tested on nearly 40 randomly selected OHNs. Test/re-test reliability was also completed. Pearson coefficients ranged from .64 to 1.00 on the dichotomous variable with 16 dilemmas having $r = .83$ or greater. Pearson coefficients for the Likert scale variable ranged from .65 to .99 with only one dilemma having a coefficient below .81.

Modification of some wording was made to further clarify the intent of items with lower

r values. The final instrument was then mailed to 353 randomly selected subjects (geographically divided) from the AAOHN mailing list. Data are currently being analyzed for final analysis.

Publications

Rogers B: An Overview of Work-Related Hazards in Nursing: Health and Safety Issues. Heart and Lung, accepted for publication, 1991

Rogers B: Occupational Health Nursing Education: Curricular Content in Baccalaureate Programs. AAOHN Journal, accepted for publication, 1991

Rogers B: Smoking Policies and Programs in Health Science Schools. Public Health Nursing, accepted for publication, 1991

Rogers B: Ethics and Research. AAOHN Journal, accepted for publication, 1990

Rogers B: Making A Case for Ethics in Occupational Health. Dangerous Properties of Hazardous Materials, accepted for publication, 1990

Rogers B: Occupational Health Nursing Practice, Education and Research: Challenges for the Future. AAOHN Journal 38:536-543, 1990

Rogers B: Occupational Health Nursing Research. Recent Advances in Nursing, 26:137-155, 1990

Rogers B: Analysis of Ethical Problems: Exposures in the Workplace. Dangerous Properties of Industrial Materials Report, accepted for publication, 1990

Rogers B: Establishing Research Priorities in Occupational Health Nursing. AAOHN Journal 37:493-500, 1989

Rogers B: Biological Hazards in Critical Care Nursing, Monograph, Health Sciences Media. 1989

Rogers B: Employment Characteristics of Nurse Practitioners. The Nurse Practitioner 14:56-63, 1989

Rogers B: Florence Nightingale and Research – The Historical Link. AAOHN Journal 37:238-239, 1989

Rogers B: AIDS and Ethics in the Workplace, Nursing Outlook 37:254-255, 1989

Rogers B: Ethical Decision-Making. Continuing Professional Education 3(20):1-8, 1989

Rogers B: Ethical Issues and AIDS. Parts I and II. Continuing Professional Education 3(15,16):1-16, 1989

Rogers B: Ethical Dilemmas in Occupational Health. Occupational and Environmental Medicine Report 2:85-88, 1988

Rogers B: HIV Infection/AIDS in the Workplace. American Association of Occupational Health Nurses, 1988

Rogers B: Perspectives on Occupational Health Nursing. AAOHN Journal 36:151-155, 1988

Rogers B: Ethical Dilemmas in Occupational Health Nursing. AAOHN Journal 36:100-105, 1988

Rogers B, Sweeting S, Davis B: Selected Work Characteristics of Nurse Practitioners. Tarheel Nurse, 50: 13-14, 1988

Safety, Industrial Relations, and Productivity

James C. Robinson, Ph.D.
University of California, Berkeley
Institute of Industrial Relations
2521 Channing Way
Berkeley, California 94720

Program Area: *Other Occupational Needs*
Grant Number: *5 K01 OH00075-03*
Start & End Dates: *09/30/88 – 09/29/91*
Funding Level: *$32,383 ($97,183 Cum)*

Importance to Occupational Safety and Health

This study will help assess the likely impact of "right-to-know" and other worker-oriented policy strategies in occupational safety and health. Using a wide range of statistical data from the 1980s, it measures worker and labor union responses to perceived workplace hazards. Particular emphasis is placed on worker turnover, the incidence and outcome of union representation elections, and labor productivity in manufacturing. Hazard-related industrial conflict is one of the most important yet least understood social consequences of unsafe and unhealthy working conditions.

Objectives

This study examines worker and labor union responses to occupational safety hazards in order to measure the association between working conditions, industrial relations, and labor productivity. Research to date, based on data from the 1970s, suggests that hazardous working conditions exert significant negative influences on the quality of industrial relations, which in turn reduces labor productivity and economic performance. This study updates and expands the existing literature, using a broad range of statistical data sources covering the 1980s.

Methodology

The study uses four different data sets to examine a number of worker and union responses to occupational hazards. Information on working conditions is obtained from the Bureau of Labor Statistics and Workers' Compensation records. Outcome variables include worker quits and desire for union representation, union success in representation elections, and measures of productivity in manufacturing industries. Multivariate statistical methods are used to isolate the independent influence of working conditions *per se* from other important determinants of these outcome variables.

Significant Findings

The 1984 AFL-CIO survey contains information on worker perceptions of workplace hazards plus industry and occupation codes by means of which objective injury risks can be matched to the survey using data from the Bureau of Labor Statistics. Measures of worker responses include: (1) reported dissatisfaction with the job; (2) intention to quit; and (3) willingness to vote in favor of union representation, should an NLRB election be held. Workers exposed to injury risks are less satisfied with their jobs, more likely to quit, and more willing to vote pro-union than are workers not exposed to hazards. These results hold strong after controlling for worker demographic variables (race, sex, education, age, etc.) and other job characteristic variables in addition to hazards (wages, fringe benefits, promotion possibilities, etc.). Compared to safe jobs, jobs presenting health and safety hazards are likely to offer low wages, few fringe benefits, poor promotion possibilities, and less job security; they are disproportionately staffed with minority workers.

Complete data on all closed union representation elections for the 1977-87 period were obtained from the National Labor Relations Board. To reduce the quantity of data to be analyzed, focus is on the 1977, 1980, 1983, and 1987 elections (approximately 15,000). The NLRB data are being used to answer two related but distinct questions concerning the influence of hazardous working conditions on the incidence and outcomes, respectively, of union representation elections. Results indicate that (1) representation elections are much more frequent in hazardous industries than in safe industries, regardless of the year examined, and (2) the probability of union victory is higher in hazardous than in safe industries, though the effect is not large and varies across years. Given the much more frequent incidence of representation elections in hazardous rather than in safe industries, documented in (1), this implies that unions, through the election mechanism, are gaining substantially more members in hazardous than in safe industries.

Turnover (quits) and strike data were obtained for individual workers over the 1985-87 period from the Panel Study of Income Dynamics (PSID). Among female workers, exposure to workplace hazards exerted a significantly positive influence on the probability of quitting, controlling for other job and demographic characteristics (wage, employment tenure, etc.). No equivalent effect was found for male workers. Workers exposed to hazards were significantly more likely to be unionized than workers not exposed to hazards. Among unionized workers, strike rates were higher in hazardous industries than in safe ones.

Publications

Robinson JC: Toil and Toxics: Workplace Struggles and Political Strategies for Occupational Health. University of California Press, in press, 1990

Microsensor Array for the Identification of Organic Vapors

Edward T. Zellers, Ph.D.
University of Michigan
School of Public Health
Department of Environmental and Industrial Health
109 South Observatory
Ann Arbor, Michigan 48109-2029

Program Area: *Other Occupational Needs*
Grant Number: *5 K01 OH00077-02*
Start & End Dates: *07/15/89 - 07/14/92*
Funding Level: *$32,070 ($63,627 Cum)*

Importance to Occupational Safety and Health

This work addresses the need for improved sensor technology in personal direct-reading monitoring equipment for organic vapors. Currently available instruments generally lack the selectivity necessary to identify a given vapor or to discriminate between the components of even simple mixtures of vapors. The successful project will yield an array of sensors capable of identifying organic vapors from several classes and differentiating the components of vapor mixtures. The small size and low power requirements of the array will facilitate incorporation into miniaturized instrumentation suitable for use in real-time personal monitoring and respirator-cartridge breakthrough applications. This, in turn, will improve capabilities for characterizing and controlling occupational exposures to hazardous chemicals.

Objectives

This study concerns the development of an array of coated surface-acoustic-wave (SAW) microsensors for the measurement of organic vapors. The microsensor array comprising sensors with partially selective responses is intended to provide response patterns that are characteristic of different vapor contaminants. Pattern recognition analysis of the multidimensional sensor-response data can then be used to determine the identity and quantity of the target vapor(s) when present alone or in mixtures with other vapors.

Methodology

A series of chemically sensitive SAW-sensor coatings will be tested for their responses to several members of each of 11 classes of organic vapors. The sensor responses will be stored and then analyzed collectively using pattern recognition methods. Following initial screening experiments, a subset of coatings will be chosen based on their ability to discriminate between different types of organic vapors. The coating materials will consist of monomeric, oligomeric, and polymeric compounds with differential absorption affinities for organic vapors. Exposure of the sensor to industrially relevant vapor mixtures will be performed to verify the results predicted from the pattern recognition analyses.

Significant Findings

Sensor responses have been characterized for up to 32 vapors on each of four coatings. Preliminary analyses indicate a high degree of discrimination even for vapors of similar structure and functionality. In addition, strong correlations have been found between the magnitudes of the sensor responses and certain physicochemical properties of the coatings and vapors. From these correlations, it appears possible to develop models for the quantitative prediction of sensor responses for untested vapors.

Biological Monitoring for Exposure to Complex Mixtures

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

Program Area: *Other Occupational Needs*
Grant Number: *5 R03 OH02555-02*
Start & End Dates: *09/30/88 - 09/29/90*
Funding Level: *$22,091 ($41,217 Cum)*

Importance to Occupational Safety and Health

An important problem in occupational health is exposure to chemical mixtures. This work developed methods for the improved assessment of mixed chemical exposure and methods of biological monitoring for mixed chemical exposure.

Objectives

This work investigated patterns of chemical exposure as measured by air samples and urinary metabolites. The short-term objective of the work was to develop improved methods for measuring exposure to complex mixtures. The work involved the analysis of air exposure data and urine metabolite data using pattern recognition techniques. The results of pattern recognition analysis have been used for the identification and quantitation of exposure. The long-term objective of the work was to reduce occupational and environmental disease by improved identification and management of chemical exposure.

Methodology

A group of workers with four different job types volunteered for this study. This work used conventional passive and active air sampling techniques plus gas chromatography/flame ionization detection (GC/FID) to measure solvents in air. In addition, an existing method of hydrolysis, extraction, and gas chromatography was used to measure metabolites in urine. The data obtained from gas chromatography were analyzed using pattern recognition and classification techniques to identify patterns of exposure (cluster analysis) and to classify exposure (classification analysis). Principal component analysis was used for cluster analysis. Classification was done with a principal component model and with Classification and Regression Tree analysis (CART).

Significant Findings

Principal component analysis has successfully identified significant patterns of solvent exposure. The loadings of peaks in the resulting principal components has identified the sources of mixed exposure. Classification of the air samples has also been accomplished using the CART techniques. Exceptions to the classification of air exposures are attributed to work practices.

Toxicological Effect of Vanadium on the Macrophage Response to Listeria Challenge

Cheng-i Wei, Ph.D.
University of Florida
Food Science and Human Nutrition Department
Gainesville, Florida 32611-0163

Program Area: *Other Occupational Needs*
Grant Number: *5 R03 OH02583-02*
Start & End Dates: *04/01/88 - 03/31/91*
Funding Level: *$21,750 ($43,500 Cum)*

Importance to Occupational Safety and Health

Vanadium-exposed workers were reported to be more susceptible to colds and other respiratory illnesses than non-exposed co-workers. It is suspected that vanadium affects host immunity and renders the workers more susceptible to infectious agents. Using mice as a model, the information obtained in this study will contribute to the understanding of the underlying mechanisms involved in vanadium toxicity and its immunomodulating activity. Most of the reported immunotoxicity studies are primarily based on analyses of macrophage viability and phagocytic activity. Information obtained can be used to help establish a more accurate workplace exposure level of vanadium. In addition, the approaches employed in this study can serve as a basis for detailed mechanistic studies of the immunotoxicological effects of other heavy metals.

Objectives

The overall goal of this project is to determine if the decreased resistance of mice to *Listeria monocytogenes* due to vanadium treatment is through interference with peritoneal macrophage (PEM) ingestion and/or processing of the pathogen, or through inhibition of the T-cell mediated recruitment of bone marrow promonocytes to the site of inflammation. The effects of vanadium treatment on the biochemical and structural aspects of mouse PEM as related to phagocytic and bactericidal functions will also be explored.

Methodology

Female $B_6C_3F_1$ mice weighing 18-20 g will be dosed IP every three days for 3 or 6 weeks with ammonium metavanadate (NH_4VO_3) solution in 0.1 M phosphate buffer (pH 7.2), NH_4Cl solution, or phosphate buffer. The doses of NH_4VO_3 will be 10.0, 5.0, or 2.5 mg/kg body weight. Three days after final challenge, the mice will be treated with *Listeria monocytogenes* for clearance studies or sacrificed for the collection of PEM. Bacterial clearance from the peritoneal cavity, spleen, and liver will be performed in mice at 0, 2, 4, 8, 24, and 48 h post-infection with 3.3×10^3 *Listeria*.

The intracellular killing of *Listeria* by PEM will also be performed. PEM from *Listeria* challenged animals will be subjected to freeze-thawing in test tubes at 0, 15, 30, or 60 min for determination of intracellular bacterial numbers on trypticase soy agar. To assay the activities of glucose-6-phosphate dehydrogenase, glutathione reductase, and glutathione peroxidase, PEM at 10^7/ml are subjected to freeze-thawing to prepare cytolysates for protein and enzyme assays. The release of β-galactosidase, lysozyme, hydrogen peroxide, leukotriene C, and interleukin-l will be determined with the appropriate methods. In addition, the superoxide anion production and the reduced and oxidized glutathione content in PEM will also be checked. The effects of vanadium treatment on macrophage cytoskeleton and macrophage membrane receptors for complement and IgG-F3 will be determined using the procedures of Solomon et al. (Cell 18:431, 1979).

Appropriate statistical analyses [analysis of variance (ANOVA), Duncan's comparison of means, and the Student's t-test] will be employed to determine the significance of vanadium treatment of the parameters investigated.

Significant Findings

Intracellular activities of PEM β-glucuronidase, N-acetyl-β-D-glucosaminidase, acid phosphatase, and lysozyme from vanadium treated animals were assayed to investigate possible reasons for the depressive effect of NH_4VO_3 on the intracellular killing of *Listeria monocytogenes* by murine PEM. Acid phosphatase activity/10^6 cells for the 2.5 and 10 mg V/kg groups was depressed by 22.8 and 44.7%, respectively, when compared to phosphate buffer controls. No significant effect was observed with the other three enzymes. Kinetic studies (*in vitro*) on the effect of NH_4VO_3 at 5, 10, 15, and 20 mM on these enzymes showed similar patterns of effect. Lineweaver-Burk analysis of acid phosphatase indicated linear non-competitive inhibition by vanadium with a K_i of 14.8 mM. NH_4Cl and 10 mg V/kg treatments also enhanced extracellular secretion of β-glucuronidase and lysozyme attributing to the presence of ammonium ion whose effects have been well established. The decrease in acid phosphatase activity might contribute, in part, through its interference in the phosphorylation/dephosphorylation reactions to the diminished intracellular killing ability of PEM.

Publications

Owusu-Yaw J, Cohen MD, Fernando SY, Wei CI: An Assessment of the Genotoxicity of Vanadium. Toxicology Letters 50:327-336, 1990

Cohen MD, Fukayama MY, Wei CI: Immunotoxicological Studies of Ammonium Metavanadate in Mice. In: Biological Monitoring of Exposure to Metals, John Wiley and Sons, Inc., in press, 1990

Wei CI, Owusu-Yaw J, Cohen MD, Fernando SY: An Assessment of the Genotoxicity of Vanadium. The Toxicologist 10:92 (Abstract 365)

Cohen MD, Chen CM, Wei CI: Decreased Resistance to *Listeria Monocytogenes* in Mice Following Vanadate Exposure: Effects Upon the Function of Macrophages. Int J Immunopharmacol 11:285-292, 1989

Wei CI, Cohen MD: *In Vivo* Vanadium Effect in the Clearance of *Listeria Monocytogenes* by Mouse Peritoneal Macrophages. Proc of the Sixth International Symposium on Molybdenum, Vanadium and Other Trace Elements held at Jena, German Democratic Republic, 1:86-92, July 3-6, 1989

Cohen MD, Wei CI: Vanadium Inhibition of Glucose-6-phosphate Dehydrogenase and Glutathione Reductase: Possible Mechanisms and Implications for Macrophage Function. Proc of the Sixth International Symposium on Molybdenum, Vanadium, and Other Trace Elements, Jena, German Democratic Republic, 1:79-85, July 3-6, 1989

Wei CI, Cohen MD: Decreased Resistance to *Listeria Monocytogenes* in Mice Following Vanadium Exposure: Effects upon the Function of Macrophages. The Toxicologist 9:17, 1989 (Abstract)

Cohen MD, Wei CI: Effect of Ammonium Metavanadate Treatment upon Murine Peritoneal

Macrophage Respiratory Burst-Related Biochemistry. FASEB J 2:A915, 1988

Cohen MD, Wei CI: Effects of Ammonium Metavanadate Treatment upon Macrophage Glutathione Redox Cycle Activity, Superoxide Production, and Intracellular Glutathione Status. J Leuko Biol 44:122-129, 1988

Sen AC, Cohen MD, Wei CI: Vanadium Inhibition of Glucose-6-phosphate Dehydrogenase and Glutathione Reductase *In Vitro*. FASEB J 2:A1819, 1988

Development of a Low-Cost Ethylene Oxide Detector

Cynthia L. Benner, Ph.D.
ADA Technologies, Inc.
304 Inverness Way South, Suite 110
Englewood, Colorado 80112

Program Area: *Other Occupational Needs*
Grant Number: *2 R44 OH02662-02A1*
Start & End Dates: *09/30/88 - 02/28/92*
Funding Level: *$396,315 ($443,222 Cum)*

Importance to Occupational Safety and Health

Regulations governing the exposure of employees to ethylene oxide (EtO) have become stricter in recent years due to studies which have established the mutagenicity and animal carcinogenicity of EtO. There is a need for a new EtO monitor because commercially available instruments and devices for measuring EtO do not address the needs of EtO users or the Occupational Safety and Health Administration (OSHA) requirements for monitoring work areas where EtO is used. The EtO monitor being developed by ADA Technologies, Inc. (ADA) will combine the low cost and low maintenance characteristics of a solid state detector-based monitor with the specificity and sensitivity of a gas chromatograph. The monitor will alert employees of EtO levels exceeding the Permissible Exposure Level, the excursion limit, and the action level.

Objectives

The goal of this research and development program is to design, build, and test a prototype EtO monitor that is versatile enough to be used as an inexpensive hand-carried portable monitor or a wall-mounted area monitor. The prototype EtO monitor will operate continuously as a direct-reading instrument, employing a rugged solid state semiconductor sensor. A gas chromatography column will provide the specificity for EtO that is lacking in existing low-cost commercial real-time monitors. The prototype will be capable of providing an updated digital concentration readout once every minute and displaying an audible/visual alarm when the EtO concentration exceeds one of two preset levels. The final instrument design will incorporate low cost components so that the anticipated price of a commercial version will not exceed $4,000.

Methodology

The Phase II research program will expand on the work performed in Phase I. At the present time, a series of experiments are being performed to optimize the EtO sensor such that EtO sensitivity is maximized and interference sensitivity is minimized. Six sensors have been set up in a test bed configuration in which the temperature and resistance of each sensor is monitored while the heater voltages of the sensors are varied. The test bed is enclosed in a temperature- and humidity-controlled test chamber into which 4 ppm EtO, a simulated air mixture, or 1000 ppm of an interfering compound flows continuously. The experiments will determine the optimum heater voltage/temperature at which the EtO signal-to-noise ratio is maximized. These experiments will also provide data on the response of the sensor to various interferences.

Testing of chromatographic parameters has also begun. Various column materials have been obtained, and these will be evaluated for ability to elute EtO in one minute or less and for ability to resolve EtO from interferences. A single sensor operating at the optimum heater voltage identified in the previous task will be housed in an insulated metal block, and the column outlet will be positioned as close to the sensor as possible. Different flow rates and column temperatures will be tested. When the proper column material and conditions have been identified, flow system parameters will be thoroughly evaluated, and a calibration procedure will be developed for the prototype instrument. Based on the results of these tasks, a prototype monitor will be assembled and tested in the laboratory. In addition, the instrument will be evaluated at various hospitals in the Denver area. Following the field testing, a preliminary

design of a final instrument configuration will be proposed.

Significant Findings

An important result of the original Phase I investigation was that EtO was measurable in a room air background at the target detection limit of 0.1 ppm. Also, dichlorodifluoromethane did not interfere with the measurement of 0.1 ppm to 7 ppm EtO. Cylinder gases were not required for either the carrier gas or as support gases for the detector. The EtO retention time was 17 seconds, with an injection time of 5 seconds and total cycle time of 3 minutes. This instrument is capable of operating continuously in a stand-alone mode.

The most significant problem with the original EtO instrument was the effect of isopropyl alcohol (IPA) on the EtO signal. Because of the non-specificity of the detector, it was necessary to improve the separation of EtO from interfering species. This was accomplished by increasing the column length from 1.5 feet to 10 feet in the re-submittal experiments. With the new column, 1 to 8 ppm EtO were easily separated from 1,000 ppm IPA and methanol. Water was also separated from EtO in the longer column, eliminating the need for the reference sensor. In the Phase II prototype EtO monitor, different methods to avoid exposure of the sensor to interferences and water will be explored. Temperature effects are not a concern with the new instrument design because the temperature of both the column and sensor block are controlled.

The Phase II program began September 1, 1990. Task 1 sensor optimization experiments are proceeding on schedule, and there are no significant findings from these experiments to report at this time.

International Conference on Ethics, Health Policy, and Epidemiology

Barbara R. Visscher, M.D., Dr.P.H.
University of California, Los Angeles
School of Public Health
Department of Epidemiology
405 Hilgard Avenue
Los Angeles, California 90024-1772

Program Area: *Other Occupational Needs*
Grant Number: *1 R13 OH02825-01*
Start & End Dates: *08/01/90 - 07/31/91*
Funding Level: *$12,380 ($12,380 Cum)*

Importance to Occupational Safety and Health

This is a request for funds to partially support an international conference on issues of ethics and health policy that arise in epidemiological practice and research. Some of these problems particularly relating to privacy, informed consent of subjects, and access to information sources have been described and discussed since the 1960s, but additional problems related to influence of sources of support on presentation of the results of studies, as well as critical review of methodologic issues, have also been recognized more recently. The International Epidemiological Association (IEA) has requested the development of a set of guidelines. This conference will provide an opportunity for broad, open discussion of the various proposed guidelines which are being put forward. The two-and-a-half days prior to the Los Angeles International Scientific Meeting of the IEA on August 5-9, 1990, will be an ideal opportunity to facilitate broad international participation in these discussions.

Funds are requested for one planning meeting, transportation, and subsistence for invited speakers and discussion leaders, and for publication of the proceedings.

GRANTS ACTIVE DURING FY90

	COMPETING GRANTS		TOTAL GRANTS	
	No. of Awards	Amount of Awards	No. of Awards	Amount of Awards
Grants from FY90 Budget ($6.897M)				
Research Project Grants (R01)	16	$2,472,209	41	$5,643,958
Career Development Grants (K01)	7	$356,569	13	$542,391
Small Grants (R03)	4	$75,407	12	$251,327
Other Grants	3	$416,315	4	$459,639
Subtotal	30	$3,320,500	70	$6,897,315
Grants from FY89 Budget ($6.196M)				
Research Project Grants (R01)	2	$193,281	16	$1,807,066
Career Development Grants (K01)	0	$0	4	$126,930
Small Grants (R03)	2	$45,584	8	$173,135
Other Grants	1	$46,820	2	$246,663
Subtotal	5	$285,685	30	$2,353,794
Grants from FY88 Budget ($6.224M)				
Research Project Grants (R01)	3	$316,759	9	$1,199,802
Career Development Grants (K01)	0	$0	2	$59,152
Small Grants (R03)	1	$21,349	4	$86,527
Other Grants	0	$0	0	$0
Subtotal	4	$338,108	15	$1,345,481
Awards from all Years				
Research Project Grants	21	$2,982,249	62	$8,650,826
Career Development Grants	7	$356,569	19	$728,473
Small Grants	7	$142,340	24	$510,989
Other Grants	4	$463,135	6	$706,302
TOTAL	39	$3,944,293	115	$10,596,590

FY90 Grant Awards By Program Area

Program Area	Competing Grants		Total Grants		
	No. of Awards	Amount of Awards	No. of Awards	Amount of Awards	Amt. Per.
Occupational Lung Diseases	5	$588,367	11	$1,045,856	15%
Musculoskeletal Injuries	5	$164,239	9	$499,578	7%
Occupational Cancers	2	$378,285	7	$822,111	12%
Traumatic Injuries	4	$192,701	8	$626,348	9%
Cardiovascular Diseases	0	$0	0	$0	0%
Reproductive Disorders	1	$253,528	2	$312,646	5%
Neurotoxic Disorders	1	$233,100	3	$520,537	8%
Noise-Induced Hearing Loss	3	$361,600	4	$403,605	6%
Dermatologic Disorders	0	$0	2	$292,936	4%
Psychologic Disorders	0	$0	1	$95,960	1%
Control Techniques	1	$81,777	4	$203,948	3%
Respirator Research	3	$258,215	5	$494,518	7%
Other Occupational Needs	5	$808,688	14	$1,579,272	23%
TOTAL	30	$3,320,500	70	$6,897,315	100%

FY90 Grant Awards By Region And State
70 Grants Totalling $6,897,315, Amounts In $1,000's

	No.	Amt.	(Per.)		No.	Amt.	(Per.)
Region I	7	$604,678	(8.8%)	Region II	10	$1,203,393	(17.4%)
Connecticut	1	$141,912	(2.1%)	New York	10	$1,203,393	(17.4%)
Massachusetts	5	$408,766	(5.9%)				
Vermont	1	$54,000	(0.8%)				
Region III	4	$740,696	(10.7%)	Region IV	7	$576,322	(8.4%)
Maryland	3	$598,762	(8.7%)	Alabama	1	$53,138	(0.8%)
Virginia	1	$141,934	(2.0%)	Florida	1	$95,757	(1.4%)
				North Carolina	5	$427,427	(6.2%)
Region V	18	$1,339,401	(19.5%)	Region VI	6	$613,760	(8.9%)
Illinois	3	$74,869	(1.1%)	Louisiana	1	$59,118	(0.8%)
Michigan	9	$929,812	(13.5%)	Oklahoma	2	$350,011	(5.1%)
Ohio	6	$334,720	(4.9%)	Texas	3	$204,631	(3.0%)
Region VII	2	$188,061	(2.7%)	Region VIII	3	$584,556	(8.5%)
Iowa	1	$40,838	(0.6%)	Colorado	2	$569,589	(8.3%)
Missouri	1	$147,223	(2.1%)	Utah	1	$14,967	(0.2%)
Region IX	9	$506,752	(7.3%)	Region X	4	$539,696	(7.8%)
Arizona	1	$21,615	(0.3%)	Alaska	1	$19,159	(0.3%)
California	8	$485,137	(7.0%)	Washington	3	$520,537	(7.5%)

Grant Number	Principal Investigator	Current Funding	Page
	Research Project Grants (R01)		
5 R01 OH00823-10	Mohamed B. Abou-Donia, Ph.D.	$162,873	85
5 R01 OH00835-12	William J. Swartz, Ph.D.	$59,118	77
3 R01 OH00978-09S1	James R. Trudell, Ph.D.	$292,338	136
5 R01 OH01122-08	Charles W. Kauffman, Ph.D.	$216,383	63
7 R01 OH01152-09S1	Donald Henderson, Ph.D.	$194,938	92
2 R01 OH01301-07	Klaus Willeke, Ph.D., CIH	$151,077	123
5 R01 OH01595-06	William C. Hinds, Sc.D.	$94,391	124
5 R01 OH01630-07	Edwin M. Uyeki, Ph.D.	$150,104	139
5 R01 OH01632-02	Neil J. Zimmerman, Ph.D.	$123,194	126
5 R18 OH01981-02	C. Scott Clark, Ph.D., P.E., CIH	$165,593	141
5 R01 OH02005-06	Philip I. Harber, M.D., M.P.H.	$76,720	127
5 R01 OH02067-07	G. Marie Swanson, Ph.D., M.P.H.	$152,499	51
3 R01 OH02091-05S1	James J. Nordlund, M.D.	$200,517	104
5 R01 OH02114-03	William W. Merrill, M.D.	$116,868	11
2 R01 OH02128-06	William W. Clark, Ph.D.	$147,223	95
2 R01 OH02132-04	Nurtan A. Esmen, Ph.D.	$68,689	112
2 R01 OH02148-06	Stephen F. Cleary, Ph.D.	$141,934	142
5 R01 OH02149-05	Ghulam A.S. Ansari, Ph.D.	$143,568	144
5 R01 OH02214-03	William E. Brown, Ph.D.	$100,008	12
2 R01 OH02221-03A1	Stephen M. Rappaport, Ph.D.	$211,904	146
5 R01 OH02230-02	Bernard C. Jiang, Ph.D.	$18,859	113
5 R01 OH02254-02	Walter F. Stewart, Ph.D.	$163,127	64
5 R01 OH02264-05	Andrew J. Ghio, M.D.	$153,757	14
1 R01 OH02277-01A2	David Warshawsky, Ph.D.	$166,651	15
5 R01 OH02288-02	Philip I. Harber, M.D., M.P.H.	$141,724	147
5 R01 OH02298-02	Kenneth D. Rosenman, M.D.	$34,068	17
2 R01 OH02317-06	Roger P. Hamernik, Ph.D.	$204,377	97
5 R01 OH02329-03	Richard P. Garrison, Ph.D.	$98,997	114
2 R01 OH02332-04	Edward H. Bergofsky, M.D.	$163,262	17
5 R01 OH02352-02	Venkat Venkatasubramanian, Ph.D.	$59,219	116
1 R01 OH02373-01A1	Walter F. Stewart, Ph.D.	$169,560	78
5 R01 OH02391-02	Nabih R. Asal, Ph.D.	$196,716	149
5 R01 OH02404-02	Steven P. Levine, Ph.D.	$114,857	150
5 R01 OH02417-03	Joseph T. Hjelle, Ph.D.	$93,942	151
1 R01 OH02421-01A1	David C. Christiani, M.D.	$78,510	19
5 R01 OH02434-03	Mohamed M. Ayoub, Ph.D.	$41,963	38
5 R01 OH02437-02	David Leith, Sc.D.	$79,702	117
5 R01 OH02540-02	John G. Casali, Ph.D.	$55,757	99
5 R01 OH02564-03	Arthur B. DuBois, M.D.	$141,912	129
5 R01 OH02571-03	Irvin Schonfeld, Ph.D.	$95,960	110
5 R01 OH02574-03	Ann H. Myers, Sc.D.	$213,159	39
3 R01 OH02591-02S1	Shihab Asfour, Ph.D.	$113,781	40
5 R01 OH02593-02	E. Neil Schachter, M.D.	$135,213	20
1 R01 OH02598-01A1	Allen A. Mitchell, M.D.	$253,528	80
5 R01 OH02601-03	Carol J. Garrett, Ph.D.	$173,274	65
5 R01 OH02611-02	Susan T. Bagley, Ph.D.	$87,311	52
1 R01 OH02614-01A1	Henry H. Emurian, Ph.D.	$26,630	75

Career Development Grants (K01)

Small Grants (R03)

☆U. S. GOVERNMENT PRINTING OFFICE: 1991/548-235/40004